THE VITAMINS

A General Survey for the Practising Pharmacist

SECOND (REVISED) EDITION

THE PHARMACEUTICAL PRESS
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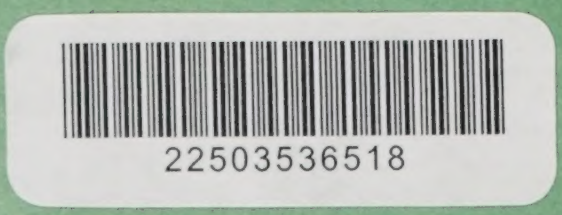

THE VITAMINS

A General Survey for the Practising Pharmacist

SECOND (REVISED) EDITION

Based on a series of articles which appeared in "The Pharmaceutical Journal" in 1938–39

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Introduction

VITAMINS may be defined as organic substances which occur in animal or vegetable tissues and are essential for the normal growth and development of man and animals and for the maintenance of bodily function and health. The vitamins do not furnish energy and are not used as materials for building up the body tissues; they are, however, necessary for the transformation of energy and for the regulation of metabolism and they are effective in small amounts. Although some animals are able to synthesise certain of the vitamins, in man this faculty is apparently restricted to vitamin D and in consequence he is dependent upon the food he eats for his supply of vitamins. It is therefore important to know what are the daily requirements of each vitamin for a young baby, a growing child and an adult. Equally it is important to know the vitamin content of the common articles of food so that a suitable diet can be selected to meet nutritional requirements. We must know, too, the signs of ill-health or other penalties that are likely to result from an insufficiency of any or all of the vitamins, and whether any ill-effects are likely to result from having too much.

It was the object of the series of articles which forms the basis of this booklet (and which appeared in THE PHARMACEUTICAL JOURNAL for August 27, September 3, 10, October 15, 29, 1938, and January 21, 1939) to present such a résumé of the subject that will enable pharmacists to answer these important questions in so far as our present state of knowledge permits. Much of the information contained in the articles is now out of date, and in consequence the whole of the material has had to be revised, especially in the light of its war-time aspects. In recent years the public has been made vitamin-minded through the activities of the advertisers of foods and medicinal articles and the subject has acquired an added significance as a result of alterations in the nation's food supply consequent upon war conditions. Appropriate action has been taken by the Ministries of Health and Food to ensure that all sections of the community are able to obtain vitamin foods or concentrates in adequate amounts for the maintenance of good health. Nevertheless the mother of a family may still wonder whether her purchases from the butcher, grocer and greengrocer provide all the food factors required in a normal diet and will ask her chemist whether it is necessary to supplement her rations with one of the medicinal vitamin preparations.

Most of our knowledge both of the existence of the vitamins and of their function has been obtained from tests on animals because for a long time this was the only method of investigation available.

As many of the vitamins have been obtained in the form of pure chemical compounds, chemical methods of investigation have become possible, with the result that chemical and physical tests are to an ever-increasing extent replacing the more laborious and less accurate biological methods, and they have made it possible to conduct direct tests for vitamin deficiency in human beings. In consequence it is possible to assess the value of vitamins to the human subject with more exactitude than when we had to rely entirely upon deductions made from observations of their effects on animals.

In the preparation of the original series of articles free use was made of the available literature, including articles and papers that had been published in *The British Medical Journal*, *The Lancet*, *The Biochemical Journal* and *The Journal of the American Medical Association*. Acknowledgment is hereby made to these, to the works of reference listed on page 54, and to all sources from which the present material has been compiled.

CHAPTER I

Terminology

BEFORE the chemical structure of any of the vitamins had been established it was customary to refer to them by letters of the alphabet; and although some of them are now denoted by names which indicate their chemical nature or physiological properties, the older alphabetical nomenclature is still in use. At the present time it is possible to classify the known vitamins as follows:—

VITAMIN A.—Axerophtol. Variously termed the growth-promoting, anti-xerophthalmic and anti-infective vitamin. The term includes vitamin A, vitamin A_2 and the pro-vitamins A, *alpha-*, *beta-*, and *gamma*-carotenes, cryptoxanthine, and several other carotenoid pigments.

VITAMIN B COMPLEX.—Some confusion still exists because different workers have used the same suffix to the letter B to denote different components of the complex, or different terms to denote the same components, but the following thirteen sub-divisions are those generally accepted:—

Vitamin B_1.—Aneurine hydrochloride, thiamine hydrochloride, torulin; the anti-beri-beri and anti-neuritic vitamin.

Vitamin B_2.—Riboflavine, lactoflavin; originally vitamin G in American terminology.

Nicotinic Acid and Nicotinamide.—In America the compounds are also known by the synonyms niacin and niacinamide. They were originally described as the P.P. or pellagra-preventing factor, but pellagra is now known to be a multiple deficiency

disease, and nicotinic acid deficiency is only one factor in its causation.

Vitamin B_3.—This is believed to be necessary for growth in pigeons; it has never been isolated but is possibly identical with the anti-dermatitis factor for chicks. (See pantothenic acid.)

Vitamin B_4.—This has been shown to be necessary for the prevention of paralysis in rats and chickens. Its existence is doubtful, and it is probably a mixture of other known components.

Vitamin B_6.—Pyridoxin, Adermin. It is necessary for the prevention of skin disease in rats.

Pantothenic Acid.—Present in liver and in liver extract and is necessary for growth and for the prevention of grey hair in rats. It is probably identical with the chick anti-dermatitis factor.

Vitamin H.—Biotin.—Said to be necessary for the prevention of dermatitis in rats and chicks.

Filtrate factor.—When given to chicks the filtrate, after removing vitamin B_1, B_2 and B_6 from yeast by adsorption, will prevent a nutritional dermatitis. It is believed to contain a number of factors, some of which, for example pantothenic acid, have recently assumed sufficient importance to be classified separately. In addition it is said to contain *Factor W*, an essential growth component for rats; *Vitamin M*, deficiency of which in monkeys is said to cause cytopenia, and mouth lesions and symptoms resembling those of pellagra; *Vitamins* L_1 *and* L_2, said to be necessary for lactation of young rats.

Choline.—A constituent of concentrates of the vitamin B complex, now considered to be an important member of the complex.

Bios.—A mixture of inositol, vitamins B_1 and B_6, β-alanine, pantothenic acid, biotin (vitamin H), and biotic acid.

Factor U.—Necessary for growth of chicks; possibly identical with vitamin B_6.

p-*Aminobenzoic acid.*—Necessary for the growth of bacteria and for the normal pigmentation of the hair of the rat. Growth-promoting for chicks.

Vitamin C.—Ascorbic acid (formerly known as cevitamic acid in American nomenclature). The antiscorbutic vitamin.

Vitamin D.—The antirachitic or calcifying vitamin includes: Irradiated ergosterol; calciferol (vitamin D_2) and irradiated 7-dehydrocholesterol (vitamin D_3), substances effective in the prevention and cure of rickets.

Vitamin E.—The anti-sterility or anti-dystrophic factor. A mixture of *alpha*-tocopherol and other related substances. Essential for reproduction in animals; its deficiency may be related to sterility in humans, and to certain forms of muscular dystrophy.

Vitamin K.—The anti-hæmorrhagic vitamin. A group of fat-soluble food constituents which prevent certain hæmorrhagic diseases in chicks, and are necessary for the formation of prothrombin

in the human. Menaphthone, B.P. (synonym, menadione) is a synthetic compound having vitamin K activity.

VITAMIN P.—Citrin, or hesperidin. A flavone or flavonol-glycoside which has an effect on the resistance and permeability of the walls of capillary blood vessels. It is closely related to vitamin C in function, and occurs with it in Hungarian red pepper and lemon juice.

CHAPTER II

Units of Measurement

IN order to obtain a uniform system for denoting the vitamin content of foods and preparations for medicinal use, the Committee on Biological Standardisation of the League of Nations Health Organisation have established units of measurement for biological tests. These units are based on the characteristic activity of a definite weight of a standard preparation of the vitamin and are indicated below. Before international units were defined various workers used their own units in order to compare the vitamin activity of different substances. Their units were generally defined in terms of the minimum daily dose for a test animal without any direct comparison with a standard substance, and consequently were subject to great variation. Although there is now a general tendency to abandon the older units in favour of the more exact international units, many of the figures concerning vitamin values for foods that have been published referred only to these arbitrary units, and it is difficult to translate such figures into international units since no exact comparison is possible. It is of interest to record that the international standard preparations are kept at the National Institute for Medical Research, Hampstead.

Vitamin A

The international unit for vitamin A is defined as the growth-promoting activity of 0·6 microgram of a standard sample of *beta*-carotene. This unit has been adopted by the B.P. and the U.S.P. One gramme of pure vitamin A contains 4,500,000 i.u. The relative values for the biological activities of carotene and vitamin A are applicable only to the specified conditions of the biological test. These two substances are not biologically equivalent for the human subject.

The method of assay for determining vitamin A potency is a biological test based upon the growth response of rats in which a state of vitamin A deficiency has been induced. The results are compared with the international standard preparation of *beta*-carotene. Other criteria by which the vitamin A activity may be

judged are the appearance of cornified epithelium in the vagina of spayed rats on a vitamin A-free diet and its rapid disappearance following vitamin A feeding.

A colorimetric method for the assay of vitamin A has been outlined by Carr and Price. In this method the blue colour developed when a solution of antimony trichloride in chloroform is added to a solution of vitamin A in chloroform is compared with standard colours in a Lovibond tintometer. The results are expressed as Lovibond units or blue units, but there is no exact method for the conversion of blue units to international units. An extension of this method is to measure the intensity of absorption of light of certain wave lengths by the blue coloured solution. The results of the Carr–Price method are less accurate than those of the biological method. Results more in agreement with biological tests are obtained by measuring the absorption spectrum of vitamin A in solution at a wave length of 328mμ. The "extinction coefficient" for a 1 cm. thickness of a 1 per cent. solution at 328mμ may be multiplied by 1600 (or more accurately by 1740) to give the approximate number of international units per gramme of the material. For this test, and for the blue-value, the unsaponifiable fraction of fish-liver oils should be used so as to eliminate substances other than vitamin A which give similar absorption.

Vitamin B_1 (Aneurine Hydrochloride)

The international unit of vitamin B_1 is the biological activity of 3 micrograms (0·003 milligram) of pure anhydrous aneurine hydrochloride. One milligram of the anhydrous compound is thus equivalent to 333 international units and 1 mgm. of the monohydrate is equivalent to 320 international units. This unit is the biological equivalent of the original international unit for B_1 which was defined in 1934 as the antineuritic activity of 10 mgm. of a standard adsorbate of the vitamin on Fuller's earth.

For the biological assay of substances containing vitamin B_1 several methods are in use; the more common tests utilise either the rat or the pigeon as the test subject. The growth-promoting effects of the vitamin on vitamin B_1-deficient rats, or the cure of polyneuritis in vitamin B_1-deficient pigeons are taken as evidence of vitamin B_1 activity. Another method depends upon the fact that the rate of the heart beat of rats is decreased by vitamin B_1 deficiency and can be restored to normal by administration of the vitamin. The effect of aneurine in promoting the growth of the fungus *Phycomyces Blakesleanus* is also used for the assay of the vitamin. A number of colorimetric chemical tests have been devised for determining the amount of aneurine present in foods and in urine. One of the most widely used is Jansen's thiochrome reaction (see page 12).

Vitamin B_2 (Riboflavine)

There is no international unit for riboflavine and quantities are usually expressed in terms of milligrams or micrograms of the pure

substance. For the biological assay of material containing riboflavine, the growth-response of rats is utilised. The growth of young rats fed on a diet free from riboflavine is arrested in a few weeks, but the addition of riboflavine to the diet causes resumption of growth. On the basis of this test a "unit" (the Sherman-Bourquin unit) has been defined as the daily amount of riboflavine necessary to promote normal growth in rats. This amount may be taken as approximately equivalent to 2·5 micrograms of riboflavine. Another method is based upon the fact that riboflavine is essential for the growth of certain bacteria, e.g. some strains of lactic acid producing bacteria. The test is usually carried out with *Lactobacillus casei* and the determination is made either by measuring the turbidity produced by the growth of the bacillus or by titrating the lactic acid formed. This method is applicable for the determination of riboflavine in blood, animal tissues, and urine. Physico-chemical methods depend upon measurement of the absorption spectrum in the ultraviolet region, or of the fluorescence of solutions under standard conditions.

Nicotinic Acid

No international standard has been set up for nicotinic acid or its amide. Since both substances are well-known crystalline compounds easily obtainable in the pure state, there is no need for such a standard. Quantities can be expressed in terms of milligrammes of nicotinic acid or nicotinamide. A biological method of assay based upon the curative effect of nicotinic acid for black-tongue disease in dogs has been used to determine the presence of nicotinic acid in foods. Titration of the lactic acid produced by the growth of *Lactobacillus arabinosus* under standard conditions furnishes a means for the quantitative determination of both nicotinic acid and the amide. Colorimetric methods for the assay of nicotinic acid in foods are based upon characteristic reactions of pyridine derivatives and are not truly specific for nicotinic acid (see p. 14).

Vitamin B_6 (Pyridoxin)

There is no international standard and quantities are expressed in terms of weight (micrograms) of pyridoxin. Biological assays are based on the growth-response of rats, the cure of the typical acrodynia type of dermatitis in rats, or on the growth-promoting action of pyridoxin on yeast and certain bacteria. Colour reactions, e.g. those produced when pyridoxin is mixed with ferric chloride, or with a phosphotungstic acid reagent, have been developed for the quantitative estimation of vitamin B_6 in foods.

Pantothenic Acid

There is no international standard and quantities are usually expressed in micrograms, although a "chick unit" and a "yeast unit" have been described. These are based on the growth-response of chicks and yeast respectively. There are no specific chemical or physical tests.

Vitamin C (Ascorbic Acid)

The international unit is the antiscorbutic activity of 0·05 mgm. of pure *l*-ascorbic acid. For biological assay guinea pigs are used and vitamin C activity is judged by determining either the amount of test material necessary to prevent or eradicate certain macroscopic signs of scurvy, or the amount necessary to prevent certain microscopic changes in the structure of the teeth. Chemical methods of assay have largely replaced the biological method for most purposes. These methods depend upon the great reducing action of ascorbic acid which may be titrated against iodine, methylene blue or the blue dye 2 : 6-dichlorophenolindophenol. When these tests are applied to food substances care must be taken to convert the non-reducing dehydroascorbic acid and any ascorbic acid bound to protein into ascorbic acid before titration. The reagent most generally used is dichlorophenolindophenol.

Vitamin D

The international unit of vitamin D is the anti-rachitic activity of 0·025 microgram of pure crystalline calciferol (vitamin D_2). There are no physical or chemical methods which can be used for the assay of vitamin D and the only method is the biological assay using rats or chicks for the test. In the curative method, calcification of rachitic bones in the test rats may be judged by X-ray examination or by staining sections of bones with silver nitrate (the "line" test). In the preventive method, calcification of the bones is judged from the weight of the ash obtained by igniting the thigh bones. With chicks, control tests are made with vitamin D_3.

Vitamin E

The international standard for vitamin E is a solution in oil of synthetic racemic α-tocopheryl acetate, containing 1 mgm. in 0·1 gm. The international unit is defined as the specific activity of 1 mgm. of the standard preparation (i.e. 0·1 gm. of the solution). The biological assay for vitamin E is carried out by fertility tests on rats. Physical tests involving measurement of absorption spectra and colour reactions are applicable to pure substances with vitamin E activity, but extracts containing the vitamin from plant and animal sources contain many other substances giving similar absorption spectra and colour reactions.

Vitamin K

No international standard for vitamin K has been adopted. Both 2-methyl-1 : 4-naphthaquinone and 2-methyl-1 : 4-naphthahydroquinone diacetate have been suggested as reference standards, since they can be obtained in pure form, and are relatively stable. A large number of different units have been used in different laboratories to express the activity of vitamin K preparations. Thayer and Doisy have defined the chick curative unit as the biological

activity of 0·5 microgram of 2-methyl-1 : 4-naphthaquinone. Another unit defined by Dam is the quantity of vitamin K per gramme body weight of chick, which when administered for three successive days is just sufficient to maintain the normal coagulation time in the blood of chicks on a vitamin K deficient diet. Values are related to a special preparation of dried spinach, 2 mgm. of which represents 1 unit. No exact comparison between these units and other units of vitamin K activity is possible, although one Thayer–Doisy unit has been estimated to be equivalent to 10 to 30 Dam units.

The biological methods for the determination of vitamin K are based upon a measurement of the clotting power of blood, either by determining the coagulation time or the prothrombin clotting time by which the actual amount of prothrombin present in blood is determined. Young chicks are used for assay purposes.

Vitamin P

No international standard for vitamin P has so far been adopted. The biological methods used for the demonstration of the presence of vitamin P are based on the belief that deficiency of vitamin P in experimental animals diminishes the resistance of the capillary blood vessels. No chemical method has been evolved by which deficiency of vitamin P can be detected.

CHAPTER III

Chemical and Physical Properties

Vitamin A

VITAMIN A has been isolated from the unsaponifiable fraction of fish-liver oils in the form of pale yellow-coloured crystals. When crystallised from methyl alcohol the crystals contain some of the solvent used and melt at 7·5° to 8° C. A pure form, crystallised from propylene glycol or from ethyl formate, melts at 63° to 64° C. It has the empirical formula $C_{20}H_{29}OH$, and is closely related to the plant pigment carotene, a hydrocarbon with the empirical formula $C_{40}H_{56}$. Carotene exists in three isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and animals. The exact extent to which this conversion takes place has not been determined but is probably dependent upon the species of animal and the form of carotene used. Of the three isomers—*alpha*, *beta* and *gamma* carotenes—the *beta* compound is the most active. Although the molecule of the *beta*-carotene can undergo hydrolysis with the formation of two molecules of vitamin A, it seems probable that the cleavage in the body does not occur symmetrically. *Alpha* and *gamma* carotenes each yield only one

molecule of vitamin A for one molecule of carotene, but the biological activity is less than that of the *beta* isomer. Probably incomplete absorption from the intestines is the reason for the variation in activity of the carotenes. Carotene is a dark yellow, or orange, crystalline, readily oxidisible substance which should be stored in an inert gas or vacuum. It is nearly tasteless and has a slight aromatic odour. In water it is almost insoluble; it is slightly soluble in alcohol, more soluble in ether, petroleum ether, fats and oils, and freely soluble in chloroform and benzene. Another plant pigment, cryptoxanthine ($C_{40}H_{35}OH$), is also converted into vitamin A in the liver.

Solutions of vitamin A and of carotene produce a blue colour when mixed with a solution of antimony trichloride and chloroform, and this reaction has been made the basis of a quantitative method for the evaluation of vitamin A by measuring the depth of the blue colour against standard coloured glasses in a tintometer. When examined spectroscopically, solutions of vitamin A show a characteristic absorption zone in the ultra-violet region of the spectrum. This property forms the basis of the spectrophotometric method for the quantitative assay of the vitamin. The three forms of carotene and cryptoxanthine differ from vitamin A itself in that they have absorption bands in the visible (blue and violet) parts of the spectrum as well as less marked bands in the ultra-violet region.

Carotene occurs in blood in colloidal combination with albumin; it exists in the spleen, liver, bone marrow, retina of the eye, corpus luteum, kidneys and subcutaneous fat. Light is necessary for its formation in plants, hence it is present in greater quantities in the green leaves of lettuce and celery than in the yellow or etiolated leaves or stems. Although a yellow colour is characteristic of all the vitamin A precursors it must not be assumed that a yellow colour is necessarily an indication of potential vitamin A activity. There are many other yellow pigments, but only the carotenoids can form vitamin A. Moreover, the precursors of vitamin A generally accompany the chlorophylls which mask their yellow colour. The vitamin A of plants is due to the presence of *alpha*, *beta* and *gamma* carotenes and to cryptoxanthine; that of animal tissues is due to both vitamin A and carotene, while fish-liver oils contain vitamin A but no carotene.

Stability.—As already stated, vitamin A and its precursors are stable to heat in the absence of oxidising agents, and the ordinary cooking processes do not destroy the vitamin A activity of vegetables. It is probable that the carotene in plants is even less labile than vitamin A itself. Foods that are grilled or roasted for long periods may suffer a rather large loss of vitamin A, but since the vitamin is not affected by boiling, foods cooked in this manner may retain their potency. Tinned foods and foods stored in the frozen state maintain their full value of vitamin A; dried and dehydrated foods, however, show considerable loss. Rancid fats have a catalytic effect on vitamin A destruction and increase the rate of oxidation

during storage. Some oils, e.g. wheat germ oil, contain compounds which delay the development of rancidity in fish-liver oils and have been used as preservatives of vitamin A activity. A small quantity of hydroquinone added to halibut-liver oil has a similar effect. Light also accelerates the destruction of vitamin A, hence cod-liver oil and other fish-liver oils should be stored in bottles of amber-coloured glass.

Vitamin B_1 (Aneurine Hydrochloride)

Vitamin B_1 (aneurine hydrochloride) may be isolated from rice polishings, yeast and other natural sources, or it may be prepared synthetically. It occurs as a white crystalline solid, which is soluble in water, glycerin and alcohol, but insoluble in oils, ether, acetone and other fat solvents. It is adsorbed from aqueous solutions by fuller's earth, silicates and charcoal. By adjusting the *p*H of the solution it is possible to separate vitamin B_1 from riboflavine (which usually occurs with it in natural sources) by selective adsorption on charcoal or silica. Animals are not able to synthesise the vitamin or to store it in any quantity, and with the exception of liver, milk, eggs and lean pork, foods of animal origin are poor sources of vitamin B_1. The empirical formula of aneurine hydrochloride is $C_{12}H_{17}N_4SOCl$, HCl. Its structural formula shows it to be a combination of a pyrimidine base and a thiazole ring. The vitamin occurs in nature as aneurine or its salts, and in combination with protein or pyrophosphoric acid. The hydrochloride crystallises with one molecule of water of crystallisation, and after drying at 105° it melts between 245° and 250° C.

Aneurine gives a number of diazo-colour reactions, some of which are useful as tests for identification and have been used as methods for quantitative assay. With diazo-benzenesulphonic acid and formaldehyde in a solution of sodium hydroxide containing sodium carbonate, aneurine produces a red coloured compound soluble in butyl alcohol. One of the most commonly used tests—the thiochrome reaction—depends upon the fact that vitamin B_1 in aqueous solution at *p*H 10 is oxidised by potassium ferricyanide to thiochrome, which exhibits a blue fluorescence; after extraction of the thiochrome with butyl alcohol the fluorescence can be determined quantitatively. This reaction is given both by free vitamin B_1 and by vitamin B_1 pyrophosphate; the thiochrome pyrophosphate is however not soluble in butyl alcohol. In order to determine the total vitamin B_1, the vitamin combined as pyrophosphate must first be liberated by digestion with pepsin, followed by digestion with diastase.

Stability.—Vitamin B_1 is fairly stable in aqueous solution in the presence of weak acids, and it is not destroyed when heated for several hours at temperatures below 100° C. in neutral or acid media, but is destroyed above 120° C. It is unstable in the presence of alkali and is rapidly destroyed by sulphite, a fact which must be

considered in relation to the preservation of fruit. Loss of the vitamin from foods is likely to occur during cooking processes owing to its solubility in water, and, with vegetables which are boiled in faintly alkaline water, the loss is increased by the action of the alkali. In spite of this, the loss of vitamin B_1 activity caused by cooking some foods has been reported to be surprisingly small, and it has been suggested that this is to be explained by the occurrence of the vitamin in combined form as an ester of pyrophosphoric acid. Solutions of pure aneurine hydrochloride may be sterilised without loss of activity by heating in an autoclave at 120° C. for half an hour.

Effect of Cooking on Vitamin B_1

Process	Meat	Processing time	Destruction of Vitamin B_1 per cent.
Frying	Beef, round	20 mins.	None
	Veal, hindquarters	20 ,,	45
	Pork and Ham	15 ,,	None
	Smoked Ham	15 ,,	10
	Pork, Ham	Medium, well-done	35
Roasting ..	Beef, round	2·5 hrs.	61
	Veal, hindquarters	2 hrs.	58
	Pork, loin	1·5 hrs.	50
Broiling	Beef, round	20 mins.	50
Baking	Pork, loin	1 hr.	50
Stewing	Beef, Heart	1 hr.	55
	Beef, Kidney	35 mins.	40

Beef tissues processed for 2 hours at 116° C. lost 70–80 per cent. of their vitamin B_1, and pork kept for nearly 2 hours at 121° C. lost the same amount. These figures are given by Elvehjem and co-workers (*J. Nutrit.*, 1939, **17**, 269; *Food Research*, 1939, **4**, 547).

Vitamin B_2 (Riboflavine)

Riboflavine is an orange-yellow crystalline substance, which is slightly soluble in water, producing solutions that have a green fluorescence. It is insoluble in chloroform, ether and other fat solvents. The crystals have no sharp melting point, but begin to darken at 240° C., and to decompose at temperatures between 274° and 282° C. The B.P. Sixth Addendum gives the melting point as 280° C. with decomposition.

The flavines are a group of yellow, water-soluble pigments widely distributed in nature. Riboflavine was first obtained from milk, and on that account is frequently referred to by the name lacto-flavin. It has been obtained from a large number of natural sources, including egg albumin, egg yolk, milk, liver, kidney, urine, malted barley, yeast, dandelion flowers, grasses, and the retinæ of fish eyes. In plants riboflavine appears to be formed in the actively growing parts, and remains there in greater quantity than elsewhere. For example, in the fresh green tops of carrots the concentration of riboflavine is about four times greater than in the roots. This is an

interesting contrast to the transference of carotene from the leaf to root. Also four compounds, closely related to but not identical with riboflavine, that have been prepared synthetically, have been shown to have some physiological activity similar to the properties of vitamin B_2.

Riboflavine can be extracted from natural sources by means of alcohol, or of acidified water, or of a mixture of these two solvents. From an acid solution the riboflavine can be separated from other substances by adsorption on to fuller's earth or other adsorbent, and re-dissolved in pyridine, in a mixture of pyridine methyl alcohol and water, or in aqueous solution of ammonia. The amount of riboflavine extracted from natural sources by such methods is only a small fraction of the total quantity present. Thus 100 mgm. of the flavine was obtained after three recrystallisations of the extractive from the whites of 33,000 eggs, but it has been estimated that this is only about 7 per cent. of the total flavine present.

The empirical chemical formula of riboflavine is $C_{17}H_{20}N_4O_6$. Its structural formula has been worked out by analysis and confirmed by synthesis to be a combination of a tricyclic aromatic nucleus with a pentose sugar—*dl*-ribose—attached to a nitrogen atom. The tricyclic nucleus is common to all flavines, and is the portion of the molecule responsible for the colour. It is a derivative of *iso*-alloxazine, which combines the properties of a substituted benzene derivative, an azine dye, and a pyrimidine compound. The pentose side chain is the portion characteristic of riboflavine. The full chemical name for riboflavine is 6-7-dimethyl-9-(*d*-ribityl)-*iso*-alloxazine. Riboflavine forms with phosphoric acid and a protein a yellow-coloured compound which functions as an oxidation enzyme. This compound is probably present in all cells of the higher animals and plants, and has an important action as a carrier of oxygen in the process of tissue respiration which will be referred to in the section on physiological action.

Stability.—Riboflavine is stable in acid solutions, but is affected by alkalis. In either acid or alkaline solution, however, it is decomposed by ultra-violet light or by strong sunlight.

Nicotinic Acid

Nicotinic acid, or pyridine-β-carboxylic acid, is an oxidation product of nicotine. It can be obtained from other sources, and has been prepared synthetically. In the form of its amide it has been isolated in crystalline form from liver concentrates. Nicotinic acid is a comparatively weak acid and solutions of its salts have a slightly alkaline reaction. Objections to the term "nicotinic acid" as suggesting its association with the poison nicotine have been made in America, and the term "Niacin" and "Niacinamide" have been proposed as synonyms for the acid and its amide.

Like other pyridine derivatives, nicotinic acid gives colour reactions when mixed in solution with cyanogen bromide and a

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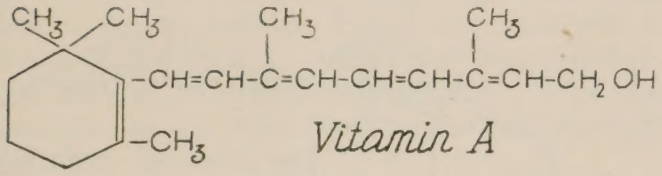
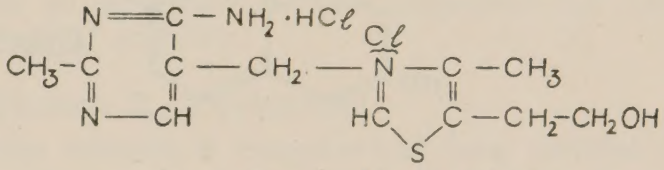
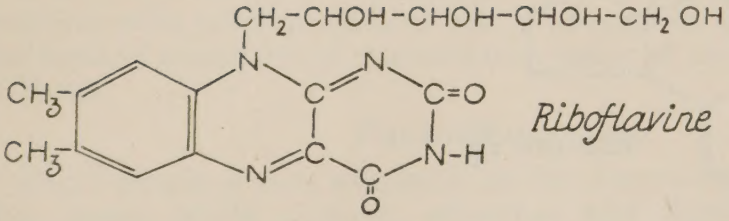


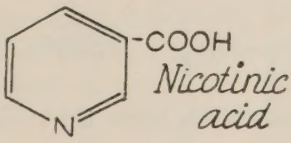
Vitamin A



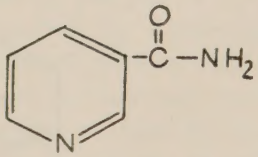
Aneurine Hydrochloride



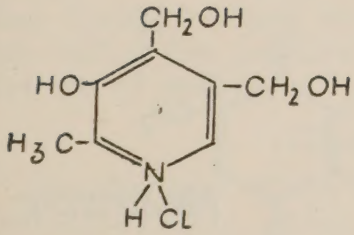
Riboflavine



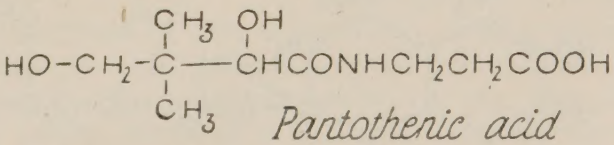
Nicotinic acid



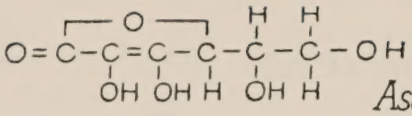
Nicotinamide



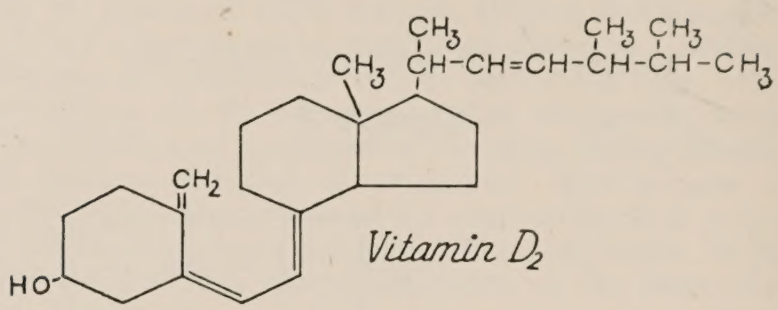
Pyridoxin



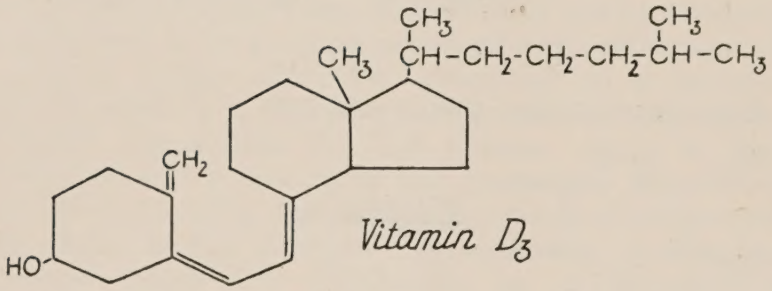
Pantothenic acid



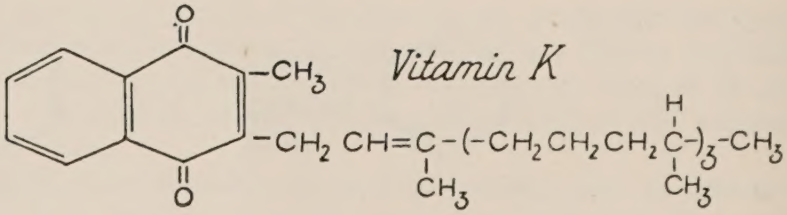
Ascorbic acid



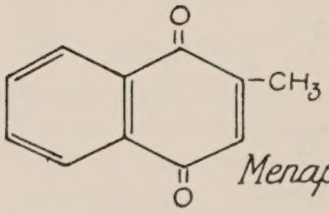
Vitamin D_2



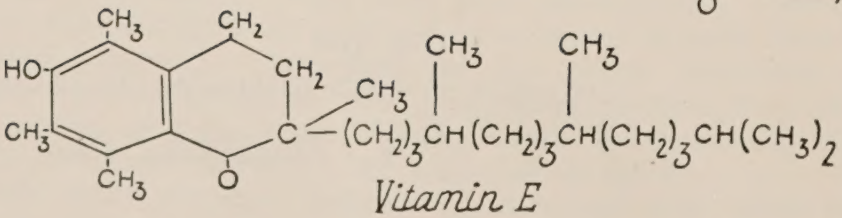
Vitamin D_3



Vitamin K



Menaphthone



Vitamin E

primary or secondary amine. The colour developed in this way with aniline or *p*-amino-acetophenone can be measured against standards in the usual way. When this test is used to determine the nicotinic acid content of foodstuffs, the latter must be completely hydrolysed to contain only the free acid. Another colorimetric test is conducted by fusing the material containing nicotinic acid or its amide with 2 : 4-dinitrochlorobenzene, extracting with alcohol and adding potassium hydroxide. This reaction, like the cyanogen reaction, is not specific for nicotinic acid since it is given by many pyridine derivatives.

Stability.—Solutions are stable at 115° C. and may therefore be sterilised by heating in an autoclave. Even moderate dry heat does not produce any loss of activity.

Vitamin B_6 (Pyridoxin)

This constituent of the vitamin B complex has been isolated in pure form, and it has also been synthesised. Pyridoxin hydrochloride is a white crystalline powder, slightly bitter in taste and odourless. Its empirical formula is $C_8H_{12}O_3NCl$. Like nicotinic acid it is a derivative of pyridine. Pyridoxin gives a diazo-colour reaction with sulphanilic acid and *p*-nitraniline and this has formed the basis of a method of quantitative assay of the pyridoxin content of foods.

Pantothenic Acid

This vitamin is now available as the dextro-rotatory calcium salt, fine, dense, white crystals, odourless and slightly bitter in taste. The empirical formula is $(C_9H_{16}NO_5)_2Ca$. It is fairly stable to moist heat, especially in neutral solution, but is destroyed by prolonged dry heat. The compound is readily hydrolysed in alkaline solution. It is widely distributed in nature, but its function in normal metabolism is not known. In animal tissues it probably occurs in combination, since proteolytic enzymes are needed to liberate it completely. Pantothenic acid is readily soluble in water. Thus its loss during cooking may be similar to that of aneurine. About one-half of the pantothenic acid in whole wheat is lost during the process of milling.

Vitamin C (Ascorbic Acid)

Ascorbic acid, which is identical with vitamin C, has the empirical formula $C_6H_8O_6$. It is a white, odourless powder which has a slightly acid taste and melts at 190° to 191° C. It is freely soluble in water and in dilute alcohol but insoluble in oils, chloroform, ether, acetone and petroleum ether. It is a powerful reducing agent and will reduce Fehling's solution in the cold. Its reducing action on the blue dye dichlorophenolindophenol is the basis of a chemical method for its estimation. In alkaline conditions ascorbic acid yields, on standing, a violet coloration with solution of ferrous sulphate. Solutions of

ascorbic acid decolorise iodine with the formation of hydriodic acid—one molecule of ascorbic acid reacting with two atoms of iodine to form two molecules of hydriodic acid, which can be estimated by precipitation as silver iodide. The product of the oxidation of ascorbic acid in this solution can be reconverted to ascorbic acid simply by evaporation.

The acid is optically active, the lævo-rotatory compound prepared by synthesis being identical in chemical and physiological properties with vitamin C obtained from natural sources. The synthetic vitamin is obtained from *d*-glucose or from *l*-xylose. Dextro-ascorbic acid is devoid of the antiscorbutic action typical of vitamin C. By the action of mild oxidising agents, ascorbic acid is converted into dehydroascorbic acid, which can function physiologically as vitamin C, and which can be reduced again to ascorbic acid. Strong oxidising agents on the other hand yield a product which has no vitamin C activity and cannot again be reduced to ascorbic acid. Determination of vitamin C by titration with reducible dyes is of value only for detecting the active ascorbic acid, it does not detect the reversibly oxidised form.

Stability.—Dry ascorbic acid is stable if stored protected from light. In the absence of oxygen, ascorbic acid in aqueous solution is fairly stable to heat, but it is unstable to heat in the presence of air or oxygen, especially in neutral or alkaline solutions, or in the presence of minute traces of copper or iron. Hence it is liable to be destroyed during the cooking of many of the foods that contain it, although the loss of vitamin C by solution in the cooking water is far greater than the loss by oxidation. Methods used for the tinning of fruits and fruit juices are generally adapted so as to minimise the loss of vitamin C. The following pre-war figures for the vitamin C content of some American canned fruit juices, when compared with the figures for fresh fruit juices on page 23, show that the sterilisation processes used permit a high degree of the vitamin activity of the original fresh juice to be retained:—

Canned fruit juice	Ascorbic acid content mgm. per 100 mils
Orange juice	31 to 56
Lemon juice	41 to 58
Grape fruit juice ..	29 to 42
Pineapple juice ..	10 to 18
Tomato juice	13 to 29

Fruit and vegetables contain an enzyme—ascorbic acid oxidase—which slowly oxidises ascorbic acid after they are gathered and more quickly after they have been cut; they should therefore not be stored too long between gathering or cutting into slices and consumption. When parsley is chopped with a sharp knife it loses about one-fifth of its vitamin C in the ensuing 30 minutes, but little

thereafter on keeping up to 3 hours. If cooking is carried out rapidly and copper or iron vessels are not used, the loss of vitamin C may not exceed 15 per cent., but if the cooking process is slow the loss may be between 30 and 40 per cent. The rate of destruction of ascorbic acid is decreased by cold storage, but drying, pickling, salting and preservation with sulphites all decrease the vitamin C activity. Green leafy vegetables and peas in the pod lose 10 per cent. of their ascorbic acid for every day they are stored after harvesting. The rate of loss in root vegetables is less rapid, but is nevertheless important because they are often stored for many months before being eaten. Potatoes which contained 16 mgm. of ascorbic acid per 100 gm. when dug in August contained only 2 mgm. per 100 gm. in the following March.

Vitamin D

Under the term "vitamin D" are included several compounds possessing the property of preventing or curing rickets. These substances are derivatives of sterols—complex compounds occurring in animal and vegetable fats—which acquire antirachitic properties when exposed to ultra-violet light. The two most important substances possessing antirachitic activity are those produced by the irradiation of ergosterol and of 7-dehydro-cholesterol.

Ergosterol is the sterol present in ergot, some fungi and moulds and in yeast. It occurs as small colourless crystals having the empirical formula $C_{28}H_{43}$ OH, usually with some water of crystallisation. It is insoluble in water, sparingly soluble in oils and freely soluble in most organic solvents. When irradiated with ultra-violet light of certain wave-lengths it undergoes a series of changes resulting in the formation of the compound termed calciferol and generally spoken of as vitamin D. The change of ergosterol into calciferol is a purely photo-chemical reaction and can occur at any temperature. There is no addition to, nor subtraction from, the ergosterol molecule, nor does polymerisation occur. There is merely a molecular rearrangement. The conversion of ergosterol into calciferol is never quantitative—even under the best conditions the product contains only about 50 per cent. of calciferol. If the irradiation is carried further—especially if the ergosterol is dissolved in alcohol—some of the calciferol is decomposed to form a compound which has been termed "substance 248," or toxisterol. The first of these names relates to the fact that the substance shows a maximum absorption of ultra-violet irradiations at a wave-length of 248 millimicrons, and the second name indicates that it is toxic. In fact, when vitamin D was first used clinically in the form of irradiated ergosterol, some of the toxic effects then reported were undoubtedly due to the presence of this product of over-irradiation. Toxisterol is not formed if the irradiation is conducted with ether as the solvent.

Cholesterol is present in many animal fats, including lanolin.

Pure cholesterol does not acquire antirachitic properties when submitted to the action of ultra-violet light. Associated with it in the natural state are small quantities of a chemical derivative of cholesterol, 7-dehydro-cholesterol. This substance has been prepared synthetically, and both the natural and the synthetic compound can be "activated," i.e. rendered antirachitic, by ultra-violet light. Activated 7-dehydro-cholesterol is the form of vitamin D produced in the skin on exposure to sunlight; it is present in milk that has been irradiated, and is the chief form of vitamin D present in fish-liver oils. This substance is termed vitamin D_3 to distinguish it from calciferol, which is termed vitamin D_2. The term vitamin D_1 is not now used, although it was at one time applied to a mixture of lumisterol and calciferol, which was then believed to be the pure vitamin D.

Crystalline esters of the vitamin prepared from some fish-liver oils are identical with the corresponding esters prepared from the synthetic vitamin. Although vitamin D_2 and vitamin D_3 have similar antirachitic values when tested on rats, they have different values when tested on young chicks—the antirachitic potency of vitamin D_3 for chicks being several times greater than that of vitamin D_2. This difference has led to some divergence of opinion concerning the value of the biological test on rats, using the international standard calciferol as a true indication of vitamin D potency. If, as suggested on p. 37, it can be accepted that vitamins D_2 and D_3 are equally effective in preventing and curing rickets in children, the rat test is reliable for a medicinal cod-liver oil, but the chick test must obviously be used for oils to be given to chicks. A third sterol derivative, 22-dehydro-ergosterol, acquires on irradiation antirachitic properties slightly less than those of vitamins D_2 and D_3. The activated compound, which is 22-dehydro-calciferol, is termed vitamin D_4; it has not yet been isolated from natural sources, but is probably present in some cereals.

Vitamin D_2 (calciferol) is not known to occur naturally; it is always artificially prepared. The precursor of vitamin D in animal tissues is not ergosterol but 7-dehydro-cholesterol. Vitamin D_3 is the naturally occurring vitamin D.

Stability.—Quantitative tests have shown that vitamin D in the form of calciferol dissolved in olive oil, cod-liver oil, halibut-liver oil or in liquid paraffin is unchanged or at most only slightly changed after fifteen to twenty months' storage. The same is true of the natural vitamin D content of both halibut-liver oil and cod-liver oil.

Vitamin E

Like vitamins A and D, vitamin E is an oil-soluble substance. It is present in the embryos of seeds, especially the embryo of wheat and in green leaves such as those of lettuce. It is present in the non-saponifiable fraction of the oils in which it occurs; it is easily oxidised and is rapidly destroyed in oils which become rancid.

Wheat-germ oil is the most commonly used source of vitamin E. The non-saponifiable fraction of this oil consists mainly of sitosterol, and when this is removed there remains a fraction having the characteristic physiological action of vitamin E. From this active fraction an alcohol of the empirical formula, $C_{22}H_{50}O_2$, has been isolated as a light yellow viscous oil. This substance, termed *alpha*-tocopherol (from *tokos*—childbirth and *phero*—to bear), has vitamin E activity to a marked degree. Two other similar compounds have been obtained from wheat-germ oil, cottonseed oil and palm oil. These are *beta*-tocopherol and *gamma*-tocopherol. These two compounds have the biological activity of vitamin E in lesser degree than *alpha*-tocopherol. All three tocopherols (*alpha*, *beta* and *gamma*) have been prepared synthetically. Altogether there are about 130 compounds which are known to have vitamin E activity.

Stability.—Vitamin E is stable at high temperatures—up to 250° C *in vacuo*—in the dry state; it is not destroyed in the ordinary processes of cooking. It is stable in light, except after prolonged exposure to ultra-violet light. It is not stable to oxidising agents, and is easily destroyed by rancid fats and by ferric chloride. Pure tocopherols are unstable in air and are destroyed by ultra-violet light. The oils in which vitamin E occurs contain compounds termed anti-oxidants, which delay or prevent the auto-oxidation of the oil and consequent rancidity. The use of wheat-germ oil—on account of the presence of these anti-oxidants—to delay the oxidation of vitamin A in fish-liver oils has been referred to previously.

Vitamin K

Vitamin K is a generic term applied to a group of naturally-occurring substances and to a number of synthetic compounds. The naturally-occurring forms of vitamin K are found in such foods as cabbage, spinach, cauliflower, tomatoes, peas, strawberries, carrots, potatoes and liver. Other sources of vitamin K which have been used in experimental work are alfalfa (lucerne) and putrefied fish meal. Vitamin K was first isolated from alfalfa as a yellow oil which is soluble in fats, inactivated by light and by oxidising agents, strong acids and alkalis. This substance was later called vitamin K_1 to distinguish it from other substances of vitamin K activity. The compound isolated from putrefying fish meal is different chemically from that obtained from alfalfa, and is termed vitamin K_2. A third substance, originally obtained from tubercle bacilli and called phthiocol has been termed vitamin K_3, but it has only very weak vitamin K activity.

These naturally-occurring forms of vitamin K are derivatives of naphthaquinone, and a number of synthetic substances of analagous chemical nature have been found to possess vitamin K activity. The synthetic substance known as vitamin K_4 is 2-methyl-1 : 4-naphthaquinone; it is official in the B.P. Sixth Addendum under the name menaphthone; in America it is known as menadione. It is

soluble in oil. When the compound is reduced in the presence of acetic anhydride, acetomenaphthone (1 : 4-diacetoxy-2-methyl-naphthalene) is formed. Acetomenaphthone, which is official in the British Pharmaceutical Codex, also has vitamin K activity. Another related synthetic compound is the sodium salt of 2-methyl-1 : 4-naphthahydroquinone diphosphoric ester, which is soluble in water. Vitamin K_5 is 4-amino-2-methyl-1-naphthol hydrochloride, also water-soluble.

CHAPTER IV

Vitamin Values of Common Foods

THE vitamin content of foods is liable to considerable variation, and values obtained by examination of one sample cannot be regarded as necessarily indicative of the vitamin content of all samples of that food. Climate, soil, methods of cultivation, time of collection and the period of storage will all affect the vitamin content of fruits and vegetables, and animal substances such as meat, milk and eggs will be affected by the food of the animal—whether green pasture or dried crops—as well as by the amount of sunshine to which the foodstuffs have been exposed. Consequently, any review of the quantitative data available must of necessity be subject to modification as a larger number of samples are examined.

The data in the accompanying tables are based on figures published by Fixsen, M. A. B., and Roscoe, M. H. (*Nutrition Abstracts and Reviews*, 1937–38, **7**, 823, and 1939–40, **9**, 795), those quoted from various authors by Bicknell, F., and Prescott, F. ("The Vitamins in Medicine," 1942), and the work on vitamin C recorded by Lampitt, L. H., Baker, L. C., and Parkinson, T. L. (*J. Soc. Chem. Ind.*, 1943, **62**, 61) and Olliver, M. (*ibid.*, p. 146). Where several values have been reported, only the lowest and highest figures are stated, while in many instances an average figure has been taken. It should not necessarily be assumed that the absence of an entry under a particular heading means that none of that vitamin is present; it may indicate that no work has been done to determine qualitatively or quantitatively the amount of the vitamin in the product. Values for vitamins A and D are stated in international units; those for carotene are given in micrograms and those for vitamin B_1, vitamin C, riboflavine, nicotinic acid and pantothenic acid in milligrammes in 100 grammes (approximately $3\frac{1}{2}$ oz.) or 100 mils of the substance. As pointed out on p. 33, the carotene in vegetables is only about one-half to one-third utilised by human beings, hence for practical purposes the number of micrograms of carotene should be divided by about 2 or 3 when calculating the biological equivalent

of vitamin A, i.e. 1 microgram of carotene = 1·7 international units, but as this is only half to one-third utilised it is equivalent to only 0·85 to 0·57 international unit, or, taking the mean, one microgram of carotene is equivalent to 0·75 international unit of vitamin A for the human being. The carotene from green leafy vegetables is more readily utilised than that from yellow vegetables such as carrots.

FRUITS	Vitamin A Int. units per 100 gm. or 100 mils	Carotene micro-gm. per 100 gm. or 100 mils	Vitamin B_1 mgm. per 100 gm. or 100 mils	Riboflavine mgm. per 100 gm. or 100 mils	Vitamin C mgm. per 100 gm. or 100 mils
APPLE*			0·12	0·005–0·03	0·1–20
Blenheim Orange					3·1
Bramley Seedling					16
Cox's Orange Pippin					1·6
APRICOT, fresh		1800–2300			1–16
,, sun dried		5100		0·057	1–2
BANANA*		124	0·09–0·18	0·0075–0·048	1–15
BLACKCURRANT	300–500				172–419
,, cooked or canned					141–183
,, jam					58
,, juice M.O.F.					140
,, puree M.O.F.					70
DATE, preserved	600		0·09		
FIG, fresh	80		0·075	0·052	2·2–8·72
,, dried			0·045–0·15		0
GOOSEBERRY			0·15		26–47
,, cooked					17·8–28·5
GRAPE		15			1–7·2
GRAPEFRUIT			0·081–0·12	0·024	41
,, canned					26–65
LEMON, juice				0·003–0·005	25–70·9
,, peel					100–205
LIME, juice		26			16·8–62·5
,, peel		305			115
LOGANBERRY, raw					20·4–48·4
,, cooked					22–26·7
MELON			0·03–0·06		1·6–20
NECTARINE	720				24
ORANGE*					58
,, juice		300–400		0·003–0·005	22–89
,, pulp			0·120		16–47
,, marmalade					7–14
PEACH, fresh		760	0·03–0·12		8–18
,, canned			0·03		3
PEAR		80	0·09	0·007–0·03	1–10
PINEAPPLE, fruit		60–160	0·075–0·1	0·013–0·13	10·4–62·9
,, canned					6·3–18
PLUM		0–230		0·025–0·044	0·5–15·0
PRUNE, dried*			0·27		2·0
RAISIN, dried			0·225		
RASPBERRY			0·075–0·105		20·3–31·7
ROSE HIP, fresh					67–459; 1400
,, ,, brought to boil					394
,, ,, boiled 5 mins. with sugar					238
,, ,, boiled 10 mins with sugar					216
,, ,, Syrup M.O.H.					175–200

* *Pantothenic Acid.*—The following fruits are reported to contain in 100 gm. the quantities of pantothenic acid indicated: apple 0·03 mgm., banana 0·07 mgm., orange 0·07 mgm., dried prune 0·06 mgm.

Tests were made by Olliver (*Lancet*, 1940, ii, 191) to determine the effect of jam-making on the vitamin content of the fruit. She obtained the following results, the figures being mgm. per 100 gm., and those in brackets being the amount in the finished product: Blackcurrant 165 (58), strawberry 65 (22), marmalade 42 (10), gooseberry 40 (11), raspberry 19 (8). The vitamin C in fruit is resistant to the effects of heat during the jam boiling process and the reduction in concentration is due mainly to dilution with sugar and water. Thus the amount of ascorbic acid in commercially prepared jams which contain 30–40 per cent. of fruit is approximately 30–40 per cent. of the amount in the fruit juice.

VEGETABLES	Vitamin A Int. units per 100 gm.	Carotene micro-gm. per 100 gm.	Vitamin B_1 mgm. per 100 gm.	Ribo-flavine mgm. per 100 gm.	Panto-thenic acid mgm. per 100 gm.	Vitamin C mgm. per 100 gm.
Artichoke, Jerusalem					0·4	9·0
Asparagus ..					0·09	30·0
Beans, runner	600		0·075–0·225			32·0
„ French		221–400		0·030–0·075		28·0
„ butter, dried			0·48			
Beetroot* ..		0	0·21	0·085	0·04	5–24
Broccoli ..	12,000				1·4	
Cabbage*† ..	900		0·075–0·42	0·05–0·215		62–105
„ boiled ..						29–45
„ steamed						44–48
Carrot† ..	2000–9600		0·18	0·02	0·2	3–7
Cauliflower, head		38	0·33			10–30
„ leaves		3300–3930				49–134
Celery ..			trace			7–13
Cucumber ..	0		0·09	0·004		13
Lentils ..		53–450	0·12–0·63	0·068		
Lettuce ..		1500–2400	0·27	0·03–0·08		5–29
Marrow ..	0		0·03–0·06			4·7–14
Mushroom ..			0·15			3·0
Onion ..		25			0·12	2·6–15
„ stewed ..			0·09–0·15			6·0
Parsley ..		3200				140–280
Parsnips ..		30	0·198			8–22
Pea		139	0·294–0·84	0·03–0·28		16–34
Potato*† ..		28–56	0·09–0·18	0·01–0·2	0·65	9–29
„ peeled, boiled			0·09			7–13
Radish ..		3	0·018–0·18	0·02		12–20
Soya Bean*† ..		450–970	0·52–1·2		1·8	
Spinach, fresh*		2630–6500	0·06	0·06–0·09	0·12	18–97
Sprouts, Brussel	12,000		0·18			71–146
„ boiled 30–40 mins.						48·9
Tomato, fresh*		14,160–35,640	0·12	0·24	1·8	12·9–39
„ tinned	4280		0·099			14–21
Turnip, root ..			0·12	0·04		17–43·4
„ tops ..						39–120
Watercress ..	12,000		0·18			89·0

* *Nicotinic Acid.*—The following vegetables are reported to contain in 100 gm. the quantities of nicotinic acid indicated: cabbage 0·3 mgm., potato 1·0–2·0 mgm., soya bean 4·8 mgm., fresh spinach 1·7 mgm., tomato (flesh) 0·5 mgm.

† *Pyridoxin.*—The following vegetables are reported to contain in 100 gm. the quantities of pyridoxin indicated: beetroot 0·11 mgm., cabbage 0·29 mgm., carrot 0·19 mgm., potato 0·16 mgm., soya bean 0·86 mgm.

BREAD AND CEREALS	Carotene micro-gm. per 100 gm.	Vitamin B_1 mgm. per 100 gm.	Riboflavine mgm. per 100 gm.	Nicotinic acid mgm. per 100 gm.	Pyridoxin mgm. per 100 gm.
WHEATEN BREAD					
Whole grain (wholemeal)		0·225–0·450	0·025–0·035		
Brown		0·15–0·24		1·2	
White (73% extraction)		0·045–0·09			
With germ, brown bread		0·24–0·27			
Ministry of Food loaf (85% extraction)		0·24–0·255			
CEREALS					
Barley*				2·5	
Oatmeal, whole grain		0·975			
,, prepared breakfast		0·42–0·81			
Rice, whole	34	0·06–0·27	0·122	4	
polished	0	0	0·08	1·6	
Sago	0				
Wheat germ*		1·8–3·75		2·7–9·1	3·5–5·0
Wheat flour, white		0·06–0·09		1·0	0·33
,, stone ground		0·48			
,, whole	102–456				0·81
Wheat flour, wholemeal bleached	43–60% loss				
Wheat flour, National wheatmeal (85% extraction)		0·3–0·36			
Semolina from durum wheat	291				
Semolina stored at room temperature	17% loss				
Spaghetti from durum wheat	52				

* *Pantothenic Acid.*—The following cereals are reported to contain in 100 gm. the quantities of pantothenic acid indicated: barley 1·0 mgm., oats (rolled) 1·1 mgm., wheat germ 0·7 mgm.

MEATS, Etc.	Vitamin A Int. units per 100 gm.	Vitamin B_1 mgm. per 100 gm.	Nicotinic acid mgm. per 100 gm.	Vitamin D Int. units per 100 gm.
MEAT				
Beef†	60			
,, lean		0·09–0·3		
,, average lean, cooked		0·072–0·24		
Kidney, beef*		0·12–0·15	16·9–19·4	
,, lamb		0·12		
,, pork		1·02	6·8–15·5	
Liver, calf	52,600–159,800		22·5	0–10
,, pig	12,600–36,700	0·27–0·468	11·8–26·5	40–50
,, lamb	6700–113,100	0·3	12·5; 45–47	20
,, ox	12,700–41,800			
,, ox, cooked		0·198–0·45		
Lamb, lean roast		0·3		
FISH				
Eels	660–18,500			474
Herrings	37–960			120–1500
Kippers				590–744
Salmon, canned†	0		6·0	200–800
Sardine	4850–54,000			1800
Oysters	420			5

* *Riboflavine.*—Beef kidney is reported to contain 0·8–2·0 mgm. of riboflavine in 100 gm.

† *Pantothenic acid.*—Canned salmon is reported to contain 0·7 mgm., and beef 1·0 mgm. of pantothenic acid in 100 gm.

DAIRY PRODUCTS	Vitamin A Int. units per 100 gm. or 100 mils	Vitamin B_1 mgm. per 100 gm. or 100 mils	Riboflavine mgm. per 100 gm. or 100 mils	Nicotinic acid mgm. per 100 gm. or 100 mils	Vitamin D Int. units per 100 gm. or 100 mils
BUTTER, English—					
Summer	2720	0·12–0·3			40–100
Winter	1540	0·03–0·09			10–30
CHEESE—					
Cheddar	5500	0			
Cheshire	×	0·09			
Gorgonzola		0·09			
EGGS, hen's					
Diet rich in carotene ..	260				
Diet poor in carotene ..	130				
Yolk		0·3–0·42	0·5–0·6	<4	
Boiled 5 minutes		0·3–0·42			
Dried		0·42			
Summer*					390
Winter					140
MILK, cow's whole—					
Average quality* (raw or pasteurised)	280–320	0·069–0·075	0·1–0·3	0·1–0·5	1·7–3·8
Jersey	470–610				
Dried, skim	0			10·5	
„ whole	428	0·21–0·27		2·5	
Human	200–500	0·025		<0·1	

* *Pantothenic Acid.*—Eggs are reported to contain 2·7 mgm. and whole cow's milk 0·28 mgm. of pantothenic acid per 100 gm. mils.

YEAST	Vitamin B_1 mgm. per 100 gm.	Riboflavine mgm. per 100 gm.	Nicotinic Acid mgm. per 100 gm.
Baker's, compressed	0·246		25·7
„ dry	0·91–3·0		12–50
„ moist		0·75–2·53	7·4–12·0
Bottom			33·9–36·7
Brewer's dry	1·8–11·4	12·4	34–93
„ moist		1·48	9·1–10·2
Faex Medicinalis B.P.			55·9–61·2
Extract	18·0		47·2–49·7

Dry brewer's yeast is reported to contain 5·18 mgm. of pyridoxin in 100 gm.

Vitamin A

Among the root vegetables the carrot has a remarkably high carotene content, it may be as much as 10,000 i.u. per 100 gm. Carrots are suitable for storing and are available for food all the year round. Green leafy vegetables—cabbage, kale, broccoli, spinach, turnip tops, and lettuce—apart from being important sources of calcium and iron, are all rich sources of carotene. Allowing for possible losses in cooking, and for the fact that the vitamin allowance must be higher when carotene is the source of vitamin A, a 3½ oz. helping of one of these greens will supply most of the daily needs of vitamin A. Apricots and peaches are also rich sources of vitamin A, the adult daily requirement being supplied by 3½ oz. of fresh or tinned apricots and by about three times as much fresh or tinned

peaches. Weight for weight dried peaches and dried apricots supply approximately three times as much of this vitamin as the fresh fruit. Dried prunes furnish appreciable amounts of vitamin A, aneurine and riboflavine. Tomatoes are also rich in carotene.

The Vitamin B Complex

It will be seen from the tables that apart from a meal containing either oatmeal, wheatmeal, or enriched bread, at least five to ten helpings ($3\frac{1}{2}$ oz. in each) of individual foods must be consumed in 24 hours to meet the minimum daily requirement of vitamin B_1. It is, therefore, not a simple task to select a diet containing adequate aneurine without the use of whole grain cereals or enriched flour and bread; moreover, significant amounts may be lost during the preparation of foods as the vitamin is readily soluble in water and easily destroyed by moist heat.

Values for the various components of the vitamin B complex in whole wheat flour and white flour are shown below; they are expressed as milligrams per 100 gm. ($3\frac{1}{2}$ oz.).

Vitamin	Whole wheat flour	White flour
Aneurine	0·48	0·07
Riboflavine	0·11	0·032
Nicotinic Acid	5·45	0·7
Pantothenic Acid	1·4	0·55
Pyridoxin	0·47	0·24

Oats rank high among the cereals as a source of the vitamin B complex and in the milling of oats the germ and the other vitamin-rich portions are left in the product used for human food. Oatmeal contains considerably more aneurine than is present in whole wheat. Oat grain contains an average of 0·126 mgm. of riboflavine, from 0·10 to 0·13 mgm. of nicotinic acid, from 2·6 to 2·9 mgm., of pantothenic acid, and from 0·15 to 0·19 mgm. of pyridoxin per 100 gm. ($3\frac{1}{2}$ oz.). It is probable that most of this vitamin content remains in the cereal after milling. The aneurine content of the potato ranges from 0·09 to 0·18 mgm. per 100 gm. ($3\frac{1}{2}$ oz.); thus, were it not for the loss during cooking, the average daily helping supplies from 8 to 14 per cent. of the adult daily requirement. Not more than about one-tenth of the daily requirement of aneurine is furnished by green vegetables, and a good deal of this is destroyed if soda is used in the cooking water.

Most of the green vegetables are also good sources of riboflavine. One helping of cooked turnip tops will supply nearly 25 per cent. of the adult daily requirements, and about half as much is supplied by spinach, kale and broccoli. Among the best sources of pyridoxin are rice, bran, liver, yeast, cereals, legumes and milk. One hundred grammes of whole wheat contains about 0·46 mgm., most meats contain 0·4 to 0·7 mgm. calculated on fresh meat, fresh vegetables about 0·1 mgm., and milk about 2 mgm. per quart.

Vitamin C in Vegetables and Fruit

In the fresh state the leafy vegetables—cabbage, broccoli, turnip tops and kale—are important sources of ascorbic acid, but loss occurs from oxidation on storage and in cooking. Probably 25 per cent. of the vitamin C of cabbage and other vegetables is destroyed by oxidation during cooking, and another 25 per cent. is lost in the cooking water. Further destruction of ascorbic acid by oxidation occurs when these leafy vegetables are bruised or chopped into small pieces and allowed to stand at room temperature, both before and after cooking. These losses can be reduced by keeping the vegetables in a refrigerator until required for cooking, by using only a small quantity of water and by raising it to the boiling point before placing the vegetables in it.

Blackcurrants and strawberries contain more ascorbic acid than oranges or lemons; and gooseberries, loganberries, raspberries and blackberries are also important sources of vitamin C. The tomato is also a good source of ascorbic acid, having an average content of 25 mgm. per 100 gm. Thus, two tomatoes supply about the recommended minimum daily allowance of 30 mgm. for the adult. The acidity of the tomato juice protects the ascorbic acid from any considerable loss in cooking, unless soda is used in the process. An apple weighing about 6 oz. may supply one-sixth of the daily requirement of ascorbic acid, but the amount of the acid present varies appreciably among the different kinds of apples. Apples can be stored and used throughout a large portion of the year when supplies of ascorbic acid from other foods are difficult to obtain. The citrus fruits are important for their ascorbic acid content; an orange weighing about $5\frac{1}{2}$ oz. will supply the adult daily requirement. A somewhat larger weight of grapefruit will do the same, so will about 6 oz. of canned grapefruit juice, while tinned pineapple contains about half as much vitamin C as is present in oranges.

Vitamin C Content of Cooked Meals

Exact information concerning the actual vitamin content of meals as served for the table is not easily obtained and in order to form an opinion as to whether the food eaten provides sufficient vitamins for the daily requirement it is usually necessary to rely upon figures calculated from tables of vitamin values such as those on pages 23 to 26. Such figures do not all allow for the loss of vitamins consequent upon storage or cooking. In a few cases an investigation of the vitamin content of meals served in canteens and restaurants has been made. The investigations have been mainly concerned with the vitamin C content since this can be determined without laborious biological tests. As might be expected the results have shown a very wide variation in the amount of ascorbic acid per meal on different days and at different seasons of the year.

At a number of restaurants and canteens in one English county the vitamin C content of the meals was examined by Wokes and

co-workers (*Lancet*, 1942, ii, 569) in the months of February to May with the following typical findings:—

Restaurant	Date	Range of ascorbic acid in mgm. per meal
A	February–May	4·5 to 45
B	April	10·5 to 65·5
C	April	9 to 21
F	April	3 to 11
I	April	20·4 to 33·5
O	May	65 to 81

The ascorbic acid in vegetable dishes served at the restaurants included in this survey varied as follows:—

Vegetable	Range of weight of helping (gm.)	Ascorbic acid mgm./100 gm.	Ascorbic acid mgm. per helping
Potato	55·5 to 300	2·0 to 14	1·85 to 21·7
Greens	34 to 124	9 to 16	5·2 to 59·8
Carrot, cooked	28 to 156	0·64 to 5·9	1·0 to 5·3
,, raw	24 to 36·5	7 to 32	4·5 to 13·3
Swede	41 to 186	7·4 to 18	4·0 to 14
Turnip	16 to 29	5·5 to 10	1·6 to 2·0
Leek	35 to 97·5	12·2 to 27	6 to 12·9
Parsnip	40·5 to 157	2·5 to 5·5	1·1 to 7·6
Beetroot	35 to 85	6 to 12	2·5 to 5·5
Vegetable soup	162 to 258	under 1 to 3	2 to 6·2

The effect of peeling, keeping and cooking on the vitamin C content of six samples of potatoes was found to give little support to the belief that vitamin C is destroyed when peeled potatoes are kept overnight:—

Potatoes	Ascorbic acid mgm./100 gm.					
Raw	18·5	17·1				
After peeling	16·5	20·0	17·2	8·9	12·8	13·3
Peeled and kept overnight	16·0	18·0	13·4	8·3	10·2	13·4
Peeled, kept overnight, cooked	15·8	9·7 (kept hot for two hours after cooking)				

That a great deal of the ascorbic acid in cooked greens is lost by solution in the water has been proved by Olliver (*Lancet*, 1940, ii, 191) who showed that compared with this loss the effect of adding baking soda was negligible. For example cabbage containing 168 mgm. of ascorbic acid per 100 gm. boiled in the presence of sodium bicarbonate retained 14 per cent., extracted by the water 54 per cent., while 32 per cent. was destroyed. When boiled without sodium bicarbonate the figures were: 16 per cent. retained, 56 per cent. extracted by the water, and 28 per cent. destroyed. Comparable figures were obtained when sodium carbonate was used, and when the experiments were conducted with sprouts, although here the proportion retained was higher.

Samples of food were taken by Macdonald (*Medical Officer*, 1943, ii, 5) on various days from meals served at schools in another English county during October and November and those at a secondary school gave the following results:—

Vegetable	Ascorbic acid		mgm. per head
	mgm. per 100 gm.	mgm. per portion	
Potato	3·35	5·1	7·2
Cabbage	4·15	2·1	
Potato	1·25	2·25	4·2
Carrots	1·95	1·95	
Potato	3·45	9·25	9·75
Peas (dried)	0·65	0·50	
Potato	0·9	1·8	19·3
Cabbage, raw	17·00	3·4	
Tomato, raw	22·00	14·1	
Potato	11·00	27·5	28·3
Carrots	1·3	0·8	

Samples taken when the food was put into the containers in the kitchen at 10.30 a.m. showed 23·2 mgm. of ascorbic acid per head, but by the time the food was eaten at 12.15 p.m. this had fallen to 7·2 mgm.; in another instance the fall in the same period was from 36·1 mgm. to 29·3 mgm. At a nursery school the total vitamin C served at the meals ranged from 2·31 to 4·22 mgm. per head. These figures suggest that the majority of children in this survey were not getting enough vitamin C to satisfy their daily requirements, yet no case of scurvy was found among them.

In another series of investigations, under a scheme devised by the Ministry of Health (*Brit. Med. J.*, 1943, ii, 477), the state of vitamin A and C nutrition was investigated among some two hundred children in a provincial town. The amount of vitamin C in the children's food was calculated from the details of their dietary intake. This was more than 30 mgm. daily in only 25 per cent., between 15 and 30 mgm. in 35 per cent., and less than 15 mgm. in 40 per cent. The state of vitamin A nutrition was deduced from the results of the biophotometer test for dark adaptation. Sixteen per cent. of the children were adjudged deficient in vitamin A, 7 per cent. were probably deficient and 15 per cent. possibly deficient. The dietary intake was less than 20 i.u. per kilo. daily in 7 per cent.; between 20 and 30 i.u. per kilo. daily in 20 per cent.; between 30 and 40 i.u. per kilo. daily in 16 per cent.; between 40 and 50 i.u. per kilo. daily in 12 per cent.; over 50 i.u. per kilo. daily in 40 per cent.

CHAPTER V

Requirements of Human Subjects

BEFORE it is possible to decide whether a given diet is sufficient to meet the body's needs in respect of vitamins, it is obviously necessary to know what are the normal requirements for each vitamin and how these may be modified by the age, weight, occupation, or environment of the subject. Information concerning the normal vitamin requirements is not easy to obtain, because there is no agreed standard as to what constitutes normal nutrition, and investigations of the extent to which vitamins are utilised in the body are difficult because of the lengthy nature of the tests involved. Most of the grosser manifestations of vitamin deficiency can be recognised easily enough, as for example the bone deformities resulting from long-continued shortage of vitamin D, or scurvy due to vitamin C deficiency. But the earlier effects, the milder symptoms resulting from partial deficiency, may escape notice if reliance is placed solely on observation of clinical signs or symptoms. The study of vitamin deficiency diseases may be approached by observing the clinical signs of malnutrition in a large section of the population in relation to the nature and quality of the food consumed by it or in relation to its spending power. Such methods leave much to the individual judgment of the observer and are likely to be inaccurate. It is far more satisfactory to employ some specific test for vitamin deficiency where such tests are available, e.g. methods involving analysis of blood or urine to determine the presence of specific vitamins.

Vitamin A

The methods for measuring vitamin A deficiency are still unreliable. Although there is some evidence that the concentration of vitamin A in the blood plasma is a more reliable indicator than the dark adaptation test, it is by no means certain that the small quantities of vitamin A in the blood can be measured accurately with the chemical and physical methods so far devised. The dark adaptation test, which has been widely used, is based on the sensitivity of the eye to light following a period spent in the dark. The principle of the test depends upon the fact that the visual purple of the retina contains a pigment—rhodopsin, which is a derivative of vitamin A. This pigment is necessary for normal vision, and is constantly bleached and inactivated by light. In states of vitamin A deficiency, regeneration of this pigment is retarded, in other words, a relatively bright light cannot be seen immediately after looking at a much brighter one. Whereas most workers consider that this method is satisfactory for measuring vitamin A deficiency, others contend that the relationship between the visual adaptation in dim light and

the state of vitamin A nutrition is not sufficiently close to justify the use of this test. It is impossible to be certain to what extent differences in recorded observations represent physiological facts, or are due to differences in technique and in the interpretation of results. Some observers have been unable to produce clinical night blindness, or even changes in dark adaptation, by keeping human beings on a diet deficient in vitamin A over a long period. Studies of dark adaption show that the daily vitamin A requirements of adults necessary to prevent night blindness are of the order of 2000 i.u. of vitamin A or 4000 i.u. of β-carotene daily for an 11 stone man.

An evaluation of the vitamin A balance in the body has been made by estimating the amount of vitamin A in the liver post-mortem. The liver of a normal well-nourished man contains from 200–400 i.u. vitamin A per gm.; and that of an infant at birth contains from 14 to 17 i.u. per gm. The antimony trichloride test applied to extracts of the livers of persons killed suddenly in accidents, or dying after operations, has shown sub-normal reserves in about 16 per cent. of cases. An analysis of the pre-war English dietary indicated that probably half of the total population of Britain received suboptimal amounts of vitamin A.

In 1937 a technical commission of the League of Nations assessed the adult's requirements for vitamin A at about 3,000 i.u. daily, an amount which can be obtained from 1 pint of milk, 1 egg, 1 oz. of butter, together with a helping of green vegetables every day. These foods would contribute about 2,000 i.u. of vitamin A with about 1,000 i.u. of carotene. The daily allowance defined by the Food and Nutrition Board of the National Research Council of America and by the Council on Foods and Nutrition of the American Medical Association are given below. These figures are considered by many authorities in this country to be much too high; even on a normal well-balanced diet of pre-war days it is unlikely that any one consumed such large amounts of vitamin A, and yet, as shown by the analysis of livers of accident cases quoted above there is no evidence of any general deficiency of vitamin A. The figures are:—

	Daily allowance, i.u.
Average man of 11 stone and woman of 8½ stone ..	5,000
Women during latter half of pregnancy	6,000
,, ,, lactation	8,000
Children under 1 year	1,500
,, 1 to 3 years	2,000
,, 4 to 6 ,, ...	2,500
,, 7 to 9 ,, ...	3,500
,, 10 to 12 years	4,500
,, over 12 years and under 15 years	5,000
Between 16 and 20 years	6,000

Most of the estimated vitamin A requirements do not distinguish between the pre-formed vitamin A and carotene, but this distinction

is of more than academic interest. Experiments carried out to determine the extent to which vitamin A and carotene are absorbed from the intestinal tract in the human subject have shown that whereas vitamin A is almost completely absorbed, not more than 50 per cent. of the carotene ingested is absorbed. As possibly there is a further loss of carotene when this is converted into vitamin A after absorption, the efficiency of carotene probably does not exceed 33 per cent. of the amount consumed in the food; thus any estimate of the requirements expressed in terms of international units of preformed vitamin A must be multiplied two or three times to obtain the equivalent number of units of carotene.

Numerous investigators have attempted to correlate the vitamin A requirements to body weight by studies on various animals and man. Fairly uniform results have been obtained suggesting a daily requirement of 40 i.u. of β-carotene, or 20 i.u. of vitamin A per kilogramme of body weight as the minimum requirements for normal growth without any clinical signs of vitamin A deficiency being shown. Three times the minimum of vitamin A and five times the minimum of β-carotene are considered necessary to ensure storage of the vitamins in the tissues and for reproduction. The war-time rationed diet of the average adult not privileged to receive additional amounts of milk and eggs probably does not contribute more than about 500 to 800 i.u. of preformed vitamin A daily, and yet after more than four years of war it is difficult to find evidence of deficiency.

The Vitamin B Complex

Aneurine.—The amount of vitamin B_1 (aneurine) excreted in the urine serves as an index of the dietary intake. Persons who excrete less than 12 i.u. per day (for a 10-stone man) and who do not show an increased excretion after one or two doses of 350 i.u. are presumed to have been receiving a diet unduly low in vitamin B_1. The amount of the vitamin excreted in the urine is about 5 to 8 per cent. of that ingested. Healthy adults, between 17 and 37 years of age, on a normal diet, excrete from 12 to 35 i.u. of vitamin B_1. Calculations of the amount of vitamin B_1 in diets that are known to have produced beri-beri show that a daily intake of 70 i.u. is insufficient to prevent beri-beri. Raising the vitamin B_1 content to 163 units reduces the number of cases of the disease, but does not entirely prevent it. A thousand cases of beri-beri in the Dutch East Indian Navy occurred on diets containing from 90 to 180 units. Diets containing 253 units of vitamin B_1 prevented the disease in natives, but not in Europeans. The amount of vitamin B_1 necessary depends not only upon the age and weight of the individual, but also upon the calorie value of the food; the consumption of large quantities of carbohydrates increases the amount of aneurine required, and large quantities of fat decrease the amount of the vitamin needed.

The quantity needed is also influenced by the rate of metabolism and the external temperature. Thus hyperthyroidism, fevers and

other conditions in which there is increased metabolism, increase the amount of aneurine needed; it is possible also that the requirements are greater for persons living in the tropics than for those in cold regions. The correct daily intake of aneurine hydrochloride cannot be stated accurately, but it is generally agreed that 1 mgm. daily is the physiological minimum for an adult receiving a diet containing 3000 calories; the optimum amount is higher than this—from 1·5 to 2·3 mgm. daily for an adult man. The requirements of children are greater in proportion to body weight than those of adults, and during pregnancy and lactation women need from three to five times the normal amount.

Riboflavine.—The human requirement of riboflavine has been estimated to be from 2·2 to 3·3 mgm. daily for an adult. During pregnancy and adolescence the amount required is probably 4 to 5 mgm.

Nicotinic Acid.—The amount of nicotinic acid needed has been assessed by the American Food and Nutrition Board as from 15 to 20 mgm. daily for an adult man consuming a diet of 2,500 calories. From a study of the diets of pellagrins and the doses of nicotinic acid required to prevent relapse, and from recent studies on the urinary excretion of nicotinic acid, trigonelline, and related substances, the daily requirements of nicotinic acid in the adult would appear to be of the order of 30 to 60 mgm. per day.

Pantothenic Acid.—Nothing definite is known about the human requirements of pantothenic acid, but on the basis of experimental evidence which shows that the needs of dogs can be satisfied by 0·10 mgm. per 100 gm. of body weight, it is assumed that the human requirement may not be much more than 5 mgm. daily.

Pyridoxin.—The human requirements of pyridoxin are not known but from animal experiments it is deduced that the daily requirement may be about 2 mgm.

Vitamin C (Ascorbic Acid)

Tests to determine the vitamin C requirement of the human subject are based upon a measurement of the resistance of the capillary blood vessels, or upon estimation of the amount of vitamin C excreted in the urine. The former test depends upon the assumption that if the intake of vitamin C is inadequate the resistance of the small blood capillaries is reduced, and when slight pressure is applied to the skin bruising results. This method has been criticised severely on the ground that there is no constant relationship between the degree of capillary fragility and the state of vitamin C nutrition, and the test may, in fact, be an indication of a deficiency of vitamin P, not of vitamin C. In the urinary excretion test it is assumed that in states of vitamin C deficiency ascorbic acid is not excreted in the urine until the deficiency in the tissues has been made good; the amount of ascorbic acid necessary to produce saturation of the tissues

is taken as an index of vitamin C nutrition. Determination may also be made of the vitamin C content of whole blood—and particularly of the white blood cells.

A review of the available data indicates that the amount of ascorbic acid recommended by various workers as the daily amount required by the average adult ranges from 10 to 50 mgm. for a minimum requirement, and 30 to 100 mgm. for an optimum requirement. The Technical Commission on Nutrition of the League of Nations recommended 30 mgm. as the minimum dose necessary for the prevention of scurvy, and the Committee on Food and Nutrition of the National Research Council of America recommended 75 mgm. as the optimum daily requirement of vitamin C for the adult. While it is widely thought by experts in Britain that 75 mgm. is an excessive amount, it is considered by others that a dose of 30 mgm. is the marginal requirement, and that larger quantities are desirable. The requirements are relatively greater in infancy and old age, and during pregnancy and lactation. A nursing mother may need as much as 100 mgm. a day in order to provide her breast-fed infant with its daily requirements of the vitamin. The requirements of vitamin C are said to be increased during the course of infectious diseases, and by hyperthyroidism. The excretion of vitamin C in the urine is increased by certain drugs, such as ammonium chloride, salicylates, atropine, aspirin, sodium bicarbonate, cinchophen, barbiturates, amidopyrine, antipyrine, adrenaline and chloroform.

The daily requirements for infants range from a minimum of 10 to 25 mgm. up to 40 mgm. as the optimum dosage. The specially high requirement of infants is important, and is reflected in the relatively high content in human milk. Human milk contains an average of 4 to 8 mgm. per 100 mils during the early months of lactation; fresh cow's milk contains only from one-sixth to half the amount present in human milk, and is still further reduced by pasteurisation. Assuming an optimum requirement of 40 mgm. per day, and that cow's milk provides a maximum of 10 mgm. of vitamin C, a bottle-fed infant requires a supplement of 30 mgm. per day. It is probable that the requirements of children are not much less than those of the adult. For vitamin C is an important factor in promoting the growth of tissues. During the growing period, therefore, children should receive more than the minimal requirements of vitamin C, and their daily intake should be increased during periods of infectious illness.

Vitamin D

As there are at present no means of detecting the presence of vitamin D in blood and excreta, data concerning the body's daily requirements of this vitamin are lacking. Furthermore, the constant synthesis of vitamin D in the skin under the influence of sunlight renders it difficult to compare quantitative clinical tests. The

information that has been amassed relates principally to the doses necessary for the prevention and cure of rickets, and should be considered in relation to the data on the effects of over-dosage discussed in the next chapter. There is, however, a fairly sensitive test for the detection of active rickets based upon a measurement of the amount of the enzyme phosphatase in the blood serum. In a patient with rickets the phosphatase content of the blood rises above normal, but falls again when the curative action of vitamin D commences. As might be expected, different observers, working with different patients under different environmental conditions, have arrived at widely differing conclusions concerning the minimum amount of vitamin D necessary to prevent rickets and to promote optimum growth in infants. This quantity has been variously assessed at between 400 and 1500 i.u. a day.

That there is no certainty about how much vitamin D children need, will be seen from the following facts. The League of Nations' Commission, 1938, stated that infants required from 400 to 500 i.u. daily, and President Roosevelt's National Nutrition Conference in 1941 endorsed a figure of 400 to 800 i.u. daily for either infants or children up to 15 years. Others have made higher estimates. According to a Committee of the British Pediatrics Association a daily intake of 500 i.u. would probably protect most full-term infants and young children from rickets, but a daily allowance of 700 units would give a wider margin of safety. The cod-liver oil compound now supplied by the Government for children under 5 years contains not less than 100 i.u. of vitamin D per gramme, and the dose recommended rises from half a teaspoonful for babies under six months to a teaspoonful, thus providing some 200 to 400 i.u. daily, a dosage which the Pediatric Association Committee consider inadequate. They also disagree with the advice to give babies under six months less than older babies, for the incidence of rickets is as great under six months as over that age, and in view of the more active growth in the early months the prophylactic requirements of vitamin D are greater. A daily allowance of 700 i.u. of vitamin D (as well as 3,500 i.u. of vitamin A) is recommended. A premature infant (birth weight under 5½-lb.) requires about twice as much vitamin D as the full-time infant. This Committee advise the same dose of 700 units daily for older children on a mixed diet, dropping to 3,500 units a week at school age, when it might be added to school milk or school dinners. The optimum dose for curing established rickets is said to be 4,500 i.u., a dose which should not be exceeded.

The requirements of adults are even less easy to assess. For a great part of the year the sun's rays are poor in ultra-violet light, and even in summer this is diminished by the curtain of smoke over towns and industrial areas. It is certain, therefore, that adults must consume vitamin D—rather than one of the pro-vitamins, as the latter can be but imperfectly utilised in the climate of Great Britain. The daily amount of this vitamin needed by an adult has

been estimated as from 250 to 700 i.u. and for women during pregnancy and lactation the amount is much higher.

From the tabulated vitamin contents of foods it will be seen that few foods contain vitamin D in any but small amounts. One quart of cow's milk containing 2·5 units per 100 gm. would furnish about 33 units—far less than even the most conservative estimate of an infant's requirements. Apart from the vitamin D formed from the sterols in the skin, the vitamin D content of the adult diet is little better. One egg provides about 50 or 60 units and three ounces of butter provide about 80 units. It is small wonder that attempts are made to increase the vitamin D content of cow's milk by irradiating the cows themselves, their milk and their fodder, and that irradiation of other foods which contain ergosterol or other form of pro-vitamin D has been introduced with a similar object. From what is said on p. 19 it will be obvious that the irradiation of foodstuffs may involve the risk of the formation of toxic substances, and is not altogether a desirable procedure. It is therefore all the more necessary that infants, children and adults should have some form of vitamin D additional to that which they receive in food.

The position has been further clouded by the conflicting statement that vitamin D from different sources has different antirachitic potency for human subjects. The compound produced by irradiating ergosterol, termed calciferol or vitamin D_2, has only about a quarter of the potency possessed by vitamin D_3, when the two compounds are tested on chicks, although they are identical when tested on rats. The question to be answered then is: "Does the human subject behave like the chick or like the rat in its reaction to vitamin D?" At first it was claimed that these two forms of vitamin D were not equally absorbed from the human intestine, but later and more carefully controlled work has led to the conclusion that they are equally effective in curing rickets in children. The difference in action may be related to the concentration of the vitamin, for it has been stated that infants cannot utilise irradiated ergosterol in concentrated form as effectively as when it is diluted to the same strength as cod-liver oil.

Vitamin E

The human requirements of vitamin E are not accurately known. Very little of the vitamin is present in the average diet since the only foods that contain appreciable amounts are green leafy vegetables and wheat germ. Symptoms believed to be due to deficiency of vitamin E, abortion and certain diseases characterised by muscular wasting, are sufficiently common to cast doubt on the assertion, sometimes made, that human beings do not require vitamin E at all.

Vitamin K

The minimum requirements of vitamin K for human subjects have not been fully determined. It has been suggested that the

requirements of vitamin K for new-born infants are extremely low and that possibly one microgram of synthetic vitamin K is a sufficient daily amount. There is no relationship between the mother's diet and the post-partum level of prothrombin of new-born infants. Apparently a diet completely adequate for the pregnant woman may not be sufficient to protect the child from the potential dangers of hæmorrhage resulting from prothrombin deficiency. It is known, however, that in most instances pure vitamin K_1 or a synthetic compound having vitamin K activity given in doses from 1 to 2 mgm. is capable of correcting deficiency of vitamin K. The exact dose necessary apparently depends on the degree of liver damage present. It is known that diarrhœa and inadequate intestinal absorption will increase the need for vitamin K.

CHAPTER VI

Effects of Overdosage

THE possibility of large or frequently administered doses of the various vitamins producing untoward effects has been discussed, especially in relation to vitamins A, B_1, C and D. In general, only with vitamin D have any serious signs of toxicity (hypervitaminosis) been reported.

VITAMIN A.—No proof has been offered that to humans large doses of vitamin A are detrimental. Doses ranging from 50,000 to 300,000 i.u. a day have been given for periods of two to six months without any apparent ill-effect. Children from 8 to 14 years of age have had large doses of carotene without developing any toxic symptoms, although one or two cases of carotenæmia have been reported from the consumption of large amounts of carotene in carrots. Diarrhœa, conjunctivitis, nose bleeding and muscular cramp induced in rats and guinea-pigs by large doses of vitamin A can be prevented by large doses of vitamin C or of thyroxine.

VITAMIN B_1.—Although a few mild signs such as loss of appetite, an increase in the *p*H of the urine and mild nervous phenomena have been stated to follow excessive doses of aneurine hydrochloride in experimental animals, there is no evidence that large doses of this vitamin are toxic to human beings. The body does not store large quantities of vitamin B_1, and any excess over immediate requirements is rapidly excreted in the urine.

RIBOFLAVINE.—It may be assumed that this constituent of the vitamin B complex can be taken in large doses without harmful effect. The evidence from which this assumption is made is based largely on rat tests in which doses at the rate of 340 mgm. per kilo. of body weight caused no injury detectable post mortem. Such doses are about one thousand times the estimated daily requirements

for these animals, and on the same ratio a man weighing 11 stones would not be harmed by a daily dose of 20 gm. of riboflavine, the amount present in 20,000 litres of cow's milk.

Nicotinic Acid.—No attempt has been reported to ascertain the maximum dose of nicotinic acid tolerated by human subjects, but it appears to be quite safe in doses up to 1·0 gm. daily. Marked flushing of the face, itching and tingling of the skin have been observed after doses of 0·05 gm. orally; these symptoms do not usually persist more than an hour or two and are not experienced if nicotinamide is given instead of nicotinic acid.

Vitamin C.—Ascorbic acid is rapidly eliminated in the urine, and toxic effects from the use of this substance are not likely to occur. This is borne out by the fact that very large doses have been given to children in the treatment of whooping cough without any apparent ill-effect.

Vitamin D.—Numerous reports assign to large doses of vitamin D a definitely toxic action on the human subject. The milder symptoms of over-dosage are stated to be nausea and vomiting, increased excretion of urine and loss of weight, but these occur only when several thousand times the therapeutic dose has been given over long periods of time. There is an increase in the amount of calcium in the circulation, and this leads to the more severe symptoms due to calcification of the blood vessels, the heart muscle and the kidneys. Some of the reported cases of toxicity may have been due to the use of irradiated ergosterol containing toxic substances such as toxisterol, and attempts to establish the maximum dose that can be tolerated before toxic symptoms arise have produced some very conflicting results. Sometimes doses equivalent to many thousand times the amount recommended as a suitable curative dose for rickets have been given to children and to adults without any toxic signs being evident; at other times symptoms have supervened after doses not significantly greater than normal.

It is probable that the toxic dose of vitamin D is in excess of 10,000 i.u. per lb. of body weight, although serious and even fatal results have followed smaller doses taken over long periods. The death of a man who had taken 2,300,000 units of vitamin D daily, i.e., at the rate of 18,000 units per kilo., was attributed to the toxic effect of the vitamin, but of twenty patients who had doses at the rate of 15,000 units per kilo. of body weight, only four showed evidence of toxicity. In five cases symptoms have appeared after doses ranging from 1500 to 3000 units per kilo., but these were considered abnormal effects and not true examples of vitamin D toxicity. Furthermore, very large doses amounting to as much as 400,000 units daily have been used in the treatment of psoriasis and of rheumatoid arthritis, and in some cases incipient symptoms of excessive dosage have been noted. Doses of 400,000 to 600,000 international units of vitamin D have been given as a single massive dose to infants of 3 months of age and repeated four to six months

later for the prevention of rickets. These large doses are said to have been tolerated and no toxic manifestations were observed. Some cases of hypervitaminosis have been reported in children, and it is evident that children with rickets are more immune to toxic effects than normal children. The toxicity of vitamin D appears to be diminished by an abundant supply of vitamin A, and the loss of weight following excessive administration of vitamin D may be prevented by large doses of vitamins B_1 and C. The damage to blood vessels consequent upon hypervitaminosis D is progressive even when the dosage is diminished and attempts are made to overcome the toxic symptoms. If large doses of vitamin D are considered necessary, they should only be given while the patient is under close observation.

Vitamin E.—No toxic reactions have been reported in cases in which small doses were administered, and large doses of wheat germ oil have given rise only to minor symptoms such as skin rashes. The danger of the production of neoplasms, after the continued ingestion of large doses of tocopherols, which has been suggested by some workers, appears to be unfounded.

CHAPTER VII

Physiological Action and Signs of Deficiency

Vitamin A

VITAMIN A is stored in the body, mainly in the liver and to a very small extent in the lungs and kidneys. The amount present in the liver is very small at birth, amounting to only 14 or 17 units per gm. but increases with age and is dependent upon the amount of the vitamin in the diet. The liver of a healthy adult contains from 200 to 400 i.u. per 100 gm. Only a few milligrams of the vitamin are required by the body daily. When large doses of vitamin A are taken by mouth, the liver is able to store an amount far in excess of the body's immediate needs, and this excess is utilised in times of vitamin A deficiency. It is on this account that the onset of symptoms of deficiency is often delayed. Chronic infections, heart disease, nephritis and other diseases of the bladder and kidneys diminish the vitamin A reserves, and a similar lowering has been said to occur in syphilitic cirrhoses of the liver.

After oral administration of vitamin A, storage reaches a maximum in three to four hours, the excess being either excreted in the faeces or destroyed. Absorption of carotene from the intestine reaches

a maximum in seven to eight hours. The absorption of vitamin A and of carotene is dependent upon the presence of fat in the intestine; and the absorption of carotene is aided by the bile salts, which however are not necessary for the absorption of vitamin A. Deficient absorption may occur in disorders of the alimentary tract which interfere with the metabolism of fat. If carotene is used therapeutically as a source of vitamin A, it should be dissolved in oil and, as a practical point, liquid paraffin should not be given at the same time, as the carotene may dissolve in the mineral oil and escape absorption. The conversion of carotene into vitamin A, which probably takes place in the liver, is a slow and variable process requiring several days for its completion. Vitamin A is not excreted by the kidneys in health, but it may be excreted during illness, especially pneumonia and chronic nephritis.

The characteristic effect of vitamin A deficiency is shown in changes in the epithelial cells which form a lining to many structures in the body. In all the organs affected, the normal epithelium is replaced by hardened (keratinised) cells which resemble those of the skin. This hardened epithelium develops in the nostrils and respiratory passages, the salivary and lachrymal glands, in the bladder and genital organs and in the conjunctiva of the eye. These changed epithelial cells accumulate in masses in the ducts of glands and in the bronchial tubes and may act as a culture medium for bacteria. The name "anti-infective vitamin" applied to vitamin A is suggestive that these changes in the lining membrane of organs lead to a lowered local resistance and may facilitate the entry of bacteria. Reports of the value of vitamin A in increasing resistance to common infections are conflicting, but on the whole justify the conclusion that the vitamin is of value only when a state of vitamin A deficiency exists. Degenerative changes in nerve cells of the brain and spinal cord have also been stated to result from vitamin A deficiency, but doubt has been cast on the rôle of vitamin A as the sole cause of the changes observed in nerve cells and nerve sheaths. There is a definite interference with the formation of enamel and dentine in the teeth—in fact, deficiency of vitamin A is probably at least as important as vitamin D in its effect on the formation of the teeth, and it probably has some influence on the structure of the gums as well. Post-mortem examination of known cases of vitamin A deficiency shows epithelial changes in the respiratory passages, pancreatic duct, uterus and salivary glands. There is much wasting of the muscles, and in children the growth of bones is retarded. The conjunctiva is hardened; the hair follicles and sweat glands are also affected, the skin is dry and rough, often with a papular eruption and pigmentation.

Apart from these specific effects, vitamin A deficiency has some general action more or less common to all nutritional defects. Growth of children is retarded, there is loss of appetite, and, in adults, interference with the reproductive processes. One of the

earliest recognisable signs of vitamin A deficiency is an interference with the pigment of the retina of the eye leading to the condition of night-blindness, possibly an important factor in the cause of road accidents at night. This is discussed more fully on page 31.

Vitamin B_1 (Aneurine Hydrochloride)

The wide distribution of vitamin B_1 in the human body suggests that it has an important rôle in the functioning of every cell, rather than in the activity of special organs or of specialised tissues. The vitamin is stored to some extent in the liver, heart and kidneys; it is also present in the brain, muscle, blood, spleen and lungs. Symptoms resulting from vitamin B_1 deficiency are associated with disturbances of the functions of the nervous system, the gastro-intestinal tract, and the blood-forming mechanism. Long-continued deficiency leads to changes in nerve fibres so that neuritis is a frequent symptom of mild or even moderate deficiency, and beri-beri, or polyneuritis, is the result of gross deficiency or complete absence of the vitamin.

The physiological function of vitamin B_1 is undoubtedly associated with carbohydrate metabolism. In combination with pyrophosphoric acid vitamin B_1 forms an ester which has the properties of an enzyme, and takes an essential part in the oxidation of carbohydrates in the body. Without vitamin B_1 the oxidation of carbohydrate is incomplete, and pyruvic acid ($CH_3 \cdot COCOOH$) accumulates in the tissues, which lose their power to take up oxygen. Vitamin B_1 in the form of its pyrophosphoric ester acts as a co-carboxylase, promoting the evolution of carbon dioxide from pyruvic acid and the uptake of oxygen by the tissues. The decreased power of the tissues to respire as a result of vitamin B_1 deficiency causes damage to the brain, kidneys and heart muscle.

The accumulation of pyruvic acid in the heart muscle leads to a slowing of the rate of the heart beat (bradycardia). A deficiency of vitamin B_1 is believed to be a potent factor causing many cardio-vascular disorders. In beri-beri, the human disease resulting from gross vitamin B_1 deficiency, there are degenerative changes in the nervous system, enlargement of the heart, and accumulation of fluid in the tissues. The first symptom is loss of appetite with pain in the stomach, constipation and a feeling of general weakness. Later peripheral neuritis develops with tenderness of the calves, numbness of the extremities, shortness of breath and palpitation. Although such severe symptoms of vitamin B_1 deficiency as beri-beri are not seen in Great Britain, many minor degrees of ill-health occur as a result of insufficiency of this vitamin in the diet. Polyneuritis not uncommonly results from vitamin B_1 deficiency during pregnancy or as a result of excessive alcohol drinking. In the latter case the alcohol so damages the mucous membrane of the stomach that utilisation of vitamin B_1 from food is impossible. Failure of the appetite is, perhaps, the most constant feature of vitamin B_1 deficiency. This is usually associated with constipation, muscular

weakness, breathlessness, palpitation, neuralgic pains, neuritis, low blood pressure, and loss of weight.

Not only is vitamin B_1 an essential factor for the proper functioning of animal tissues, it is of fundamental importance to the physiological processes of plants. It promotes alcoholic fermentation by yeast, it is essential to the growth of the embryos of seeds, and influences root production. Plants are able to synthesise vitamin B_1 if supplied with those compounds used in its artificial synthesis. It has been said that the vitamin is essential for the development of a variety of micro-organisms, for the growth of the lower and higher plants, and for insects as well as for all higher animals.

Vitamin B_2 (Riboflavine)

In nature, riboflavine may occur as such, as riboflavine phosphate or as a constituent of specific flavoproteins. These flavoproteins function as important enzymes in tissue respiration. Enzymes known to contain riboflavine include cytochrome reductase, *d*-amino-acid-oxidase, and xanthine oxidase. A definite reduction in the tissue concentration of the latter enzymes has been observed in riboflavine-deficient animals. Apart from retarded growth in young animals, other symptoms of aribоflavinosis include dermatitis and cataract in rats and characteristic paralysis in chicks. Both acute and chronic riboflavine deficiency have been studied in dogs. On a diet very low in this vitamin a characteristic collapse syndrome and sudden death are observed in six to eight weeks. Prolonged subsistence on a diet low in riboflavine leads to neurological abnormalities accompanied by myelin degeneration of peripheral nerves, and the posterior columns of the spinal cord. Opacities of the cornea may occur in the dog as well as in the rat. In man, the symptoms of riboflavine deficiency include inflammation of the lips, fissures at the corners of the mouth, glossitis, dermatitis and vascularising keratitis. The ocular symptoms appear to be very constant and may appear before other symptoms of deficiency.

Nicotinic Acid

In the body, nicotinic acid functions as a component of two important coenzymes, coenzyme 1, or cozymase, and coenzyme 2, which are concerned in both glycolysis and respiration. These two coenzymes are similar in structure, differing only in the number of phosphoric acid units. Coenzyme 1 is a diphosphopyridine neucleotide, and coenzyme 2 is a triphosphopyridine neucleotide. In nicotinic acid deficiency it is possible to demonstrate a decrease in cozymase content of the liver and muscle tissue. The earliest symptoms of human pellagra are weakness, lassitude, anorexia and indigestion, and these are later followed by sore and ulcerated mouth, diarrhœa and a typical dermatitis which affects the hands, face and neck. Nicotinic acid is widely used in the treatment of human pellagra, but it is most successful when given in conjunction with

other factors of the vitamin B complex or by means of foods containing this vitamin.

Vitamin B_6 (Pyridoxin)

The mechanism by which pyridoxin functions in the living organism is unknown, but like the other fractions of the vitamin B complex it may act in concert with enzyme systems. There is some evidence of a functional relationship between this vitamin and unsaturated fatty acids, and it has been suggested that pyridoxin brings about the synthesis of fat from proteins. Pyridoxin has been shown to be essential for the rat, chick, dog and pig. An acrodynia characterised by œdema, swelling, and alopecia of the paws and areas around the mouth, and frequent thickening of the ears is associated with pyridoxin deficiency in the rat. Pyridoxin deficiency in dogs results in a microcytic hypochromic anæmia. Experimental feeding of pigs has shown that deficiency of pyridoxin leads in these animals also to a severe anæmia with an accumulation of iron in the blood serum, the spleen, liver and bone marrow. This anæmia can be cured by the administration of pyridoxin. Fits resembling epilepsy are also produced by pyridoxin deficiency in pigs, and also can be prevented by giving pyridoxin. Although the anæmia has some points of resemblance to certain types of anæmia in the human subject there is, at present, no evidence for assuming that anæmias due to pyridoxin deficiency occur in man, but the experimental results indicate that pyridoxin has some influence on the blood-forming organs and on the nervous system. In fact, no clear-cut symptoms resulting from pyridoxin deficiency in the human subject have been described. Pellagra patients, treated with nicotinic acid, riboflavine and aneurine have been said to show additional improvement when pyridoxin was subsequently given. Satisfactory healing of the typical lesions of cheilitis have been ascribed to vitamin B_6 therapy. Some clinical reports have attributed improvement in Parkinson's disease, muscular dystrophy and in paralysis agitans to the administration of pyridoxin, but the results are not sufficiently definite to associate any of these conditions with pyridoxin deficiency or to ascribe to this substance any specific therapeutic rôle.

Panthothenic Acid

The constituent of the vitamin B complex, formerly termed "filtrate factor" which prevents dermatitis in chicks, has now been identified as pantothenic acid. Deficiency of pantothenic acid in the diet of rats leads to necrosis of the adrenal cortex; greying of the hair has also been recorded. In dogs, pantothenic acid deficiency is characterised by sudden collapse associated with decreased blood sugar, increased non-protein nitrogen and lowered blood chloride. Severe intussusception in the intestinal tract and fatty livers have also been observed. Changes in the spinal cord have been seen in

chicks and in pigs fed on synthetic diets of low pantothenic acid content.

Vitamin C (Ascorbic Acid)

Ascorbic acid is stored in the body and is found in all tissues and body fluids. The greatest amount is present in the cortex of the suprarenal gland with lesser amounts in other gland tissues, the lens of the eye, the liver, spleen, kidneys and muscles. The amount present in the blood influences the strength of the capillary blood vessels in the skin, and in states of vitamin C deficiency there is a tendency to bleeding on slight pressure or injury. The classical disease resulting from vitamin C deprivation is scurvy, which has become extremely rare since the value of fresh vegetables and, particularly, of fruit juices, has been recognised. A less marked form of vitamin C deficiency, termed latent or sub-acute scurvy, sometimes occurs in infants and young children.

Vitamin C is probably an important factor in connection with resistance to bacterial infection and toxins. During tuberculosis, diphtheria, typhoid, pneumonia, whooping cough and some other infections, the needs of the body for vitamin C are greatly increased, and it has been claimed that ascorbic acid injected intravenously or given by mouth in large doses is an important auxiliary treatment of these diseases. A state of vitamin C deficiency continued over a long period is believed to be a contributory cause of rheumatic fever. Vitamin C is also considered to be an important factor in reducing the toxic effects of arsphenamine and similar arsenical compounds, gold salts, lead salts, sulphonamides, cinchophen and some other poisonous compounds.

Vitamin C fulfils an important function in connection with the formation of the intracellular cement substance—collagen—in the tissues of animals and man. It is thus necessary for the repair of wounds, the formation of bone, cartilage and the dentine of teeth and for maintaining the integrity of the capillary blood vessels.

Since deficiency of vitamin C leads to structural changes in the teeth of animals this fact has been utilised as a method of biological assay. It is possible that infections of the gum margins with tendency to bleeding and pyorrhœa may be signs of vitamin C deficiency in human subjects. Evidence of vitamin C deficiency is seen, also, in the slow healing of bones after fractures.

Ascorbic acid is one of the substances necessary for the normal formation of red blood cells, and its deficiency may lead to some forms of anæmia.

Vitamin D

Vitamin D is necessary for the absorption and retention of calcium and phosphorus, and for the maintenance of normal calcium and phosphorus values in blood and tissues. It is thus of great importance for the proper formation of the bony skeleton. Without a sufficiency

of vitamin D, calcium salts are not deposited in the bones, which therefore become soft and rickets results. Similarly, insufficiency of calcium in the teeth leads to their decay. Children with rickets may absorb both calcium and phosphates, but these are excreted and not utilised for bone formation. Vitamin D prevents this loss from excretion by the intestine, and although it is not definitely known how this effect is produced, it is possible that the vitamin causes a change in the reaction of the contents of the intestine favouring absorption and retention of these bone-forming substances. Vitamin D also has the property of restoring to the bone structure an important enzyme, phosphatase, which is able to convert organically combined phosphorus into a diffusible inorganic form and thus to raise the concentration of phosphates in the blood serum to a point where calcium phosphate is precipitated and bone is formed. It was at one time thought that vitamin D exerted its action through the medium of the parathyroid glands, but this may not be so. Vitamin D increases the amount of calcium in the blood serum by promoting absorption from the intestine—the parathyroid hormone increases the amount of calcium in the blood by drawing on the reserves in the body.

Vitamin E

Although direct proof of the effects of vitamin E on the physiological processes in the human species is lacking, there are strong grounds for believing that deductions made from animal experiments are applicable to man. As with other vitamins, knowledge of the existence and function of vitamin E arises from the result of experiments on rats, which show that a deficiency of this vitamin leads to sterility in both sexes. Female rats deficient in vitamin E do not lose the power of conception when mated with a normal male, but the effect of the deficiency is exerted at first on the fœtus and not on the reproductive organs of the mother. Changes occur in the embryo—the blood supply to the fœtus is cut off and the fœtus finally dies and is resorbed from the uterus, after which there may be permanent damage to the reproductive organs. In male rats the effects of vitamin E deficiency are to cause changes in the germ cells—the spermatozoa become mis-shapen and lose their viability.

The means by which the effects of vitamin E deficiency are brought about have not been definitely established, but it has been shown that in states of vitamin E deficiency changes occur in the structure of the anterior lobe of the pituitary gland, and probably lead to imperfect secretion of the sex-stimulating hormones. If the deficiency of vitamin E is insufficient to cause the death and resorption of the fœtuses, the litter may be born alive, but within a few days the young animals become paralysed.

As a result of these experimental observations on rats, vitamin E in the form of preparations made from wheat-germ oil have been

used in the treatment of sterility in cattle, and a good measure of success has been reported in cows that had been sterile before the treatment was given. The wheat-germ oil is given either by mouth or by injection, subcutaneously or intramuscularly. Vitamin E probably influences the hatchability of the eggs of poultry, and on that account it is used by poultry farmers to increase the fertility of their stock.

Although it cannot be said that there is positive evidence of vitamin E deficiency as a cause of sterility or of miscarriages in women, it is a common practice of obstetricians to administer a concentrate of wheat-germ oil or whole wheat germ, or α-tocopherol to women during pregnancy if they have previously had miscarriages from no accountable cause. Results of such treatment are of definitely satisfactory nature. Vitamin E preparations are also given in other disturbances of the reproductive system, including sterility in both sexes, menstrual disturbances and toxæmias of pregnancy. As a deficiency of vitamin E in some animals, e.g., rabbits, guinea pigs, dogs, etc., has been shown to lead to degeneration of muscles and in the rat to a degeneration of nervous tissues, it has been used in the treatment of certain neuro-muscular disorders in the human—amyotrophic lateral sclerosis and various muscular dystrophies. The results of some workers support the belief that these disorders are caused by vitamin E deficiency; other workers, however, have obtained less convincing results.

Vitamin K

The exact mode of action of vitamin K has not yet been fully elucidated but it has been suggested that it acts as a reversible oxidation-reduction catalyst. It is known, however, that the vitamin is associated in some way with the integrity of the liver tissue and with the metabolism of prothrombin. The presence of adequate amounts of bile salts is required for the proper absorption of vitamin K. Liquid paraffin administered with meals may prevent the proper absorption of this vitamin as in the case of other fat-soluble vitamins. Vitamin K is not stored easily in the body, but the small amount that is retained is stored in the liver. The vitamin is not excreted in the urine; it can be demonstrated in the fæces although it is not known whether this is because the fæces contain organisms in which vitamin K is normally present, or whether vitamin K taken by mouth is in fact excreted in the fæces. The vitamin is associated intimately with the normal physiological function of the liver and with the proper coagulation of the blood. It is necessary for the proper formation of prothrombin, but how this takes place has not been determined. A deficiency of vitamin K from any cause produces a deficiency of prothrombin in the circulating blood and in all instances (except when severe liver damage is present) this deficiency of prothrombin can be corrected by proper administration of substances possessing vitamin K activity.

Vitamin P

Vitamin P, or citrin, was originally described as a compound of the flavone type present in extracts of Hungarian red pepper and lemon juice. In physiological function it is allied to vitamin C, and appears to have an effect on the resistance and permeability of the capillary walls. Two flavone dyes, hesperidin and eriodictin, are now believed to be present in citrin and to take part in an enzyme system. There is some diversity of opinion concerning the physiology of vitamin P, some workers claim that capillary fragility results from a deficiency of ascorbic acid alone, whereas others maintain that the damage to the capillaries is due to a combined deficiency of ascorbic acid and citrin. Preparations of hesperidin (or of citrin) have been used for the treatment of certain human diseases, the purpuras, in which there is a tendency to subcutaneous hæmorrhage but clinical evidence of its value is conflicting.

Biotin

Biotin is a cyclical derivative of urea now believed to be identical with the fraction of the vitamin B complex formerly called vitamin H or coenzyme R. It is a stable compound, not destroyed by autoclaving in the presence of strong mineral acids, and in the form in which it occurs in foodstuffs it is only slowly destroyed by strong alkali. The pure substance, which has been isolated, has the empirical formula $C_{10}H_{16}O_3N_2S$ and is unstable in the presence of alkali. Although biotin has for some time been recognised as necessary for the growth of bacteria, its possible rôle in the nutrition of animals and man is only just beginning to be studied. The compound is widely distributed in foodstuffs, the most important sources being liver, kidney, yeast and egg yolk.

It has been known for some time that uncooked egg-white contains a protein, avidin, which forms a complex compound with biotin. When large amounts of dried egg-white are given by mouth to rats, a characteristic dermatitis develops, and the animals lose weight and become partially paralysed. This condition is known as egg-white injury and is believed to be due to the avidin combining with the biotin in the diet and preventing its absorption. A state of biotin deficiency in human volunteers has been induced by giving large amounts of raw or dried white of egg; the symptoms included a scaly dermatitis, ashen-grey pallor, numbness of the skin and nausea. A case of biotin deficiency showing a similar dermatitis has been described of a man whose principal diet was six dozen raw eggs a week (and one to four quarts of wine daily); the dermatitis largely disappeared after two weeks' hospital diet and injections of the methyl ester of biotin. These results seem to afford clear evidence that biotin is an essential food factor for human beings, but biotin deficiency as a result of the action of egg-white occurs only when the raw or dried egg-white is eaten uncooked and in large amounts for a long time; it is unlikely to occur on the war-time egg allocation.

Biotin is present in the tissue of cancer tumours and is probably essential for its growth.

Inositol

Inositol is a hexa-hydroxy-*cyclo*hexane, isomeric with *d*-glucose. It is an extremely stable substance, resisting treatment with strong acids and alkalis. In plants it occurs as a calcium magnesium salt of inositol phosphoric acid termed "phytin." In the animal body it is found in muscle (muscle sugar), brain, red blood cells, and tissues of the eye. No information is available concerning the possible function of inositol in human nutrition. It is said to cure alopæcia in the mouse, to promote growth in rats and chicks, and to prevent certain fatty changes in the liver of rats.

p-Aminobenzoic Acid

Although this substance is usually included as part of the vitamin B complex, it is probably not correctly so classified according to the generally-accepted definition of the word "vitamin." Following the observation that greying of the fur of rats fed on a synthetic diet could be cured by the administration of 3 mgm. of *p*-aminobenzoic acid, the possibility of its use for restoring the hair pigments in the human subject has aroused attention. There is no clinical evidence to substantiate its function in this respect, and from the clinical standpoint the chief interest in *p*-aminobenzoic acid is to be found in the fact that it inhibits the action of sulphonamide compounds by interfering with enzyme action.

CHAPTER VIII

Pharmaceutical Preparations

VITAMINS are represented in the British Pharmacopœia, 1932, by cod-liver oil, emulsion of malt and cod-liver oil, and solution of irradiated ergosterol. By additions effected through the various Addenda the list has been considerably extended. As a source of the fat-soluble vitamin A the B.P. recognises in place of cod-liver oil any suitable fish-liver oil or blend of fish-liver oils, or a preparation made from the unsaponifiable matter separated from the glycerides of such oils, a concentrate prepared by partial saponification, distillation, or extraction of such oil, or by distillation or extraction of such unsaponifiable matter, or by any other suitable method. The same or similar material, and calciferol, are the officially-recognised sources of vitamin D. Fish-liver oils or concentrates made from them, high in vitamin A or D potency may be diluted to the required strength with a suitable vegetable oil, such as arachis oil, and when mixed form "vitaminised oil," now supplied as a substitute for cod-liver oil.

B.P. Preparations

Preparation	Units per Gramme	Dose
Liq. Vitamin. A Conc.	50,000 units vitamin A	0·06 to 0·3 mil equiv. to 2,500 to 12,500 units vitamin A
Calciferol	40,000 units vitamin D in 1 mgm.	*Prophylactic* (Daily) for an infant 0·025 to 0·05 mgm. = 1,000 to 2,000 units *Therapeutic* (Daily) for an infant 0·05 to 0·075 mgm. = 2,000 to 3,000 units
Liq. Calciferol (replaces Liq. Ergosterol. Irrad.)	3,000 units vitamin D	*Prophylactic* (Daily) for an infant 0·3 to 0·6 mil = 1,000 to 2,000 units *Therapeutic* (Daily) for an infant 0·6 to 1 mil = 2,000 to 3,000 units
Liq. Vitamin. D Conc.	10,000 units vitamin D	0·03 to 0·2 mil. Approx. equiv. to 250 to 1,500 units vitamin D
Liq. Vitamin. A et D Conc.	50,000 units vitamin A; 5,000 units vitamin D	0·06 to 0·3 mil. Approx. equiv. to vitamin A 2,500 to 12,500 units; vitamin D 250 to 1,250 units
Ol. Vitamin	1,000 units vitamin A; 100 units vitamin D	*Prophylactic* 1 to 2 mils = 1,000 to 2,000 units vitamin A, 100 to 200 units vitamin D *Therapeutic* 3 to 6 mils = 3,000 to 6,000 units vitamin A, 300 to 600 units vitamin D
Ol. Hippogloss. (Halibut-liver oil)	Not less than 30,000 units vitamin A	0·06 to 0·3 mil = 1,500 to 7,500 units vitamin A
Ol. Morrh.	Not less than 600 units vitamin A or less than 85 units vitamin D	*Prophylactic* 1 to 2 mils three times daily *Therapeutic* 3 to 6 mils three times daily

Preparation	Strength	Dose
Emuls. Ol. Morrh. ..	50% Cod-liver oil	*Prophylactic* 2 to 4 mils = 1,000 to 2,000 units vitamin A and 100 to 200 units vitamin D *Therapeutic* 6 to 12 mils = 3,000 to 6,000 units vitamin A and 300 to 600 units vitamin D
Emuls. Ol. Vitamin ..	50% Vitaminised oil	As for Emuls. Ol. Morrh.
Ext. Malt. c. Ol. Vitamin	10% w/w (approximately 15% v/v) vitaminised oil	4 to 16 mils. Approx. equiv. to 650 to 2,500 units vitamin A and 65 to 250 units vitamin D

Preparation	Units per Gramme	Dose
Pulv. Vitamin. B_1 ..	100 units vitamin B_1	*Prophylactic* (Daily) 1 to 2 gm. = 100 to 200 units *Therapeutic* 2 to 6 gm. = 200 to 600 units
Aneurin. Hydrochlor.	320,000 units vitamin B_1	*Prophylactic* (Daily) 0·3 to 0·6 mgm. = 100 to 200 units *Therapeutic* (Daily) 0·6 to 1·8 mgm. = 200 to 600 units
Acid. Nicotin. ..	——	0·05 to 0·1 gm.
Nicotinamid. (Nicotinic acid amide)	——	0·02 to 0·1 gm.
Riboflav.	——	0·001 to 0·01 gm.
Acid. Ascorb. ..	20,000 units vitamin C	*Prophylactic* (Daily) 0·025 to 0·05 gm. = 500 to 1,000 units *Therapeutic* 0·1 to 0·25 gm. = 2,000 to 5,000 units
Acetomenaphthon. ..	(Given by mouth)	0·01 to 0·06 gm.
Menaphthon.	(A solution in a fixed oil is injected intramuscularly)	0·005 to 0·01 gm.

B.P.C. Preparations

Some of the preparations in the foregoing list are identical with or closely resemble similar preparations of the British Pharmaceutical Codex. Thus the Codex 1934 included emulsion of cod-liver oil, halibut-liver oil, solution of vitamin A, and extract of malt with vitamins, all of which in slightly modified form have now been accepted by the Pharmacopœia. The following is a list of the vitamin-containing preparations of the Codex 1934 and its several supplements which are not included in the Pharmacopœia.

NAME	VITAMIN STRENGTH	DOSE
Emuls. Ol. Arach. (Marylebone Cream, Improved)	300 units antirachitic activity in 1 fl. dr.	4 to 8 mils
Emuls. Ol. Morrh. c. Glycerophosph.	50% Cod-liver oil	8 to 30 mils
Emuls. Ol. Morrh. c. Hypophosph.	50% Cod-liver oil	8 to 30 mils
Emuls. Ol. Morrh. c. Creosot.	33·3% Cod-liver oil	8 to 30 mils
Emuls. Ol. Vitamin. c. Glycerophosph.	50% v/v Vitaminised oil	8 to 30 mils
Emuls. Ol. Vitamin. c. Hypophosph.	50% v/v Vitaminised oil	8 to 30 mils
Emuls. Ol. Vitamin. c. Creosot.	33·3% v/v Vitaminised oil	8 to 30 mils
Ext. Malt. c. Vitamin. ..	Approx. 3,000 units vitamin A and 225 units vitamin D per fl. dr. (about three times as potent as Ext. Malt. c. Ol. Morrh.)	8 to 30 mils
Vitamin A & D Concentrates	Not standardised. Approx. 200 times vitamin content of original oil	——
Tab. Calciferol. Co. ..	500 units vitamin D per tablet	1 or 2 tablets
Cerevis. Ferment. (Yeast) ..	Contains vitamin B complex. Not standardised	8 to 16 gm. of compressd yeast. 2 to 4 gm. of dried yeast
Ext. Malt.	Contains vitamin B complex. Not standardised	4 to 16 mils
Rose Hip Syrup	200 mgm. ascorbic acid per 100 mils	Prophylactic (child) 4 to 8 mils
Tocopheryl. Acetat. ..	——	0·003 to 0·01 gm.

N.W.F. Preparations

The following vitamin preparations are included in the National War Formulary, 2nd edition.

NAME	VITAMIN STRENGTH	DOSE
Caps. Liq. Vitamin. A et D Conc.	4,500 units vitamin A and 450 units vitamin D	1 to 2 capsules a day
Caps. Ol. Hippogloss. ..	4,500 units vitamin A	——
Tab. Acid. Ascorb.	5 mgm.	Prophylactic (child)
	50 mgm.	Therapeutic
Tab. Acid. Nicotin.	50 mgm.	——
Tab. Aneurin. Hydrochlor. ..	3 mgm.	——
Tab. Calc. c. Vitamin D ..	Same as Tab. Calciferol. Co. B.P.C.	——

U.S.P. Preparations

The twelfth revision of the Pharmacopœia of the United States of America, which became official on November 1, 1942, has standards for a number of vitamin-containing preparations, including fish-liver oils and vitaminised oil, and preparations made from them, as well as for tablets of ascorbic acid, nicotinic acid, menadione (synthetic vitamin K) nicotinamide, riboflavine and thiamine hydrochloride. The U.S.P. supplies standards for a prepared oil containing natural vitamin A, a concentrated preparation of vitamins A and D, and a diluted preparation of the two vitamins of which the average dose is 2 fl. drs. These preparations are the U.S.P. equivalents of the B.P. Liq. Vitamin. A. Conc., Liq. Vitamin. A and D Conc. and Ol. Vitamin. respectively. For those who prefer it the U.S.P. gives a specification for non-destearinated cod-liver oil, the vitamin potency of which is the same as that of ordinary cod-liver oil from which part of the stearin has been removed. The question of taste can be solved by the addition of not more than 1 per cent. of a recognised flavouring agent of the U.S.P.

Storage

The loss of vitamin A in cod-liver oil emulsions on storage seems to depend more on the conditions and duration of storage than on the method of preparation of the emulsion. Protection against light, heat and air is essential. The emulsion must be kept in well-filled brown bottles, and it is desirable that the temperature should not exceed 15° C. for at higher temperatures the loss of vitamin A may be rapid. The presence of those essential oils usually added for flavouring does not affect the stability. Samples of the emulsion stored in completely-filled containers or (as prescribed by the U.S.P. for non-destearinated cod-liver oil) in contact with an inert gas, lost less than 10 per cent. of their vitamin A activity in fourteen months; in the presence of air the whole of the vitamin A may be decomposed in the same period. The British Pharmacopœia directs that cod-liver oil, halibut-liver oil, vitaminised oil and the solutions of vitamins A and D shall be stored in well-filled, well-closed containers and protected from light. Preparations of vitamin K must be kept in the dark. The U.S.P. XII goes further and directs that certain oleovitamin preparations should be preserved in small, tight containers or bottled or packaged in containers from which the air has been expelled by the production of a vacuum or by an inert gas.

Ointments and Dressings

Cod-liver oil is credited with bactericidal activity against certain micro-organisms, including *Bact. coli*, staphylococci and *B. pyocyaneus*, and this activity is said to be increased by irradiation of the oil with ultra-violet light. Dressings soaked in cod-liver oil or covered with an ointment containing 25 per cent. of cod-liver oil

have been used for infected wounds, ulcers and burns. Ointments containing zinc oxide, lanolin, soft paraffin, etc., in addition to cod-liver oil, have been used and these undergo loss of vitamin A rapidly. Suitable anti-oxidants are hydroquinone (0·2 per cent.) or tri-ethanolamine (0·2 per cent.). A fairly generally prescribed ointment is made from:

Kaolin	100 gm.
Zinc oxide	100 gm.
Cod-liver oil	100 gm.
Soft paraffin (yellow)	700 gm.
Triethanolamine	2·5 gm.

The loss of activity over a period of three months in an ointment prepared to this formula was not more than 25 per cent.

For application to the eyes in the treatment of some forms of conjunctivitis and corneal ulcers, halibut-liver oil, solution of vitamin A or vitaminised oil is often ordered as eye-drops; the oils used for this purpose must be free from acidity. Damage to the cornea of the eye caused by liquid mustard gas has been treated by means of a mixture of cod-liver oil and glucose. To 100 mils of an emulsion of cod-liver oil prepared with 1 per cent. of sodium carbonate, 4 mils of pituitary (posterior lobe) extract and glucose are added. It has not been proved that the good results obtained are due to vitamin A.

Injections

Aneurine hydrochloride is usually given orally in tablet form or parenterally in solution. A solution suitable for injection may be made by dissolving the aneurine hydrochloride in sterilised distilled water and adding sodium chloride to make the solution isotonic; e.g. aneurine hydrochloride 0·01 gm., sodium chloride 0·0075 gm., chlorbutol 0·005 gm., sterile distilled water to 1 mil; or aneurine hydrochloride 0·05 gm., sodium chloride 0·00365 gm., chlorbutol 0·005 gm., sterile distilled water to 1 mil. The B.P. Codex (Third Supplement) states that solutions for injection may be sterilised by heating with a bactericide or by filtration.

Ascorbic acid is generally given orally in tablet-form or as rose hip syrup, blackcurrant purée or concentrated orange juice. For parenteral injection a solution of the acid in sterile distilled water neutralised to *p*H 5·5–5·9 by sodium hydroxide is preferable to the acid itself. The solution, which must be freshly prepared, may be sterilised by filtration. The fat soluble vitamins A and D, also vitamin K, may be prepared for intramuscular injection by dissolving in a suitable vegetable oil, e.g. arachis oil and sterilising by heat.

Vitamins and Purchase Tax

The application of Purchase Tax to vitamin preparations produces some anomalies. In general, vitamins intended for taking by mouth are classified as "foods" and are exempt from Purchase Tax, but preparations for injection are medicines and pay tax at the rate of

16⅔ per cent. Thus tablets of aneurine hydrochloride or of ascorbic acid are not liable to the tax, but ampoules of solutions of the same substances are liable. Cod-liver oil, simple cod-liver oil emulsions, and extract of malt with cod-liver oil, have been specifically exempted, but an emulsion containing hypophosphites is liable to tax. Similarly, exemption is given to halibut-liver oil, vitaminised oil, halibut-liver oil with malt, vitaminised oil with malt, vitaminised oil emulsion, vitaminised glucose, and vitaminised foods generally, unless put up for medicinal or veterinary use. Tocopherol acetate (synthetic vitamin E) is also chargeable with Purchase Tax only when put up for injection, but acetomenaphthone and menaphthone (vitamin K substitutes) are chargeable with tax in all circumstances. Nicotinic acid, nicotinamide, and riboflavine are classed as vitamins for purposes of Purchase Tax.

Labelling

Vitamin preparations classified as medicines must be labelled to comply with the Pharmacy and Medicines Act, 1941; that is to say the label must state the B.P. or B.P.C. name (or other accepted scientific name) of the active ingredients together with the quantity present. Those vitamin preparations classed as foods will be subject to the new regulations regarding the description and labelling of foods when these come into operation.

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CHAPTER IX

The Potency of Commercial Preparations

THE following table of proprietary vitamin preparations has been compiled from information supplied by the manufacturers, and is intended to serve as a guide to the nature, potency and source of the preparations listed. The particulars concerning the potency of the preparations are the claims made by the manufacturers—no attempt has been made by THE PHARMACEUTICAL JOURNAL to verify them by actual tests on the products themselves. It is understood that in a number of instances the strengths stated are minimum claims, and the actual potency may be higher than these minimum figures show.

Values for vitamins A and D are denoted in terms of international units (i.u.); values for vitamin B_1 are usually denoted by milligrams of the pure vitamin B_1 hydrochloride (aneurine). Vitamin B_2 preparations are denoted by weight for preparations containing pure nicotinic acid and riboflavine, but the Sherman unit is used in several instances for preparations which contain the vitamin in the form of unfractionated extracts. Vitamin C is denoted as weight in grammes of pure *l*-ascorbic acid. For vitamin E various methods of expressing the potency are in vogue as the international standard of reference and international unit have only lately been adopted. Readers desiring further particulars concerning any of these preparations should communicate with the manufacturers.

Name of Preparation	Description	Makers
	VITAMIN A	
ALPHALIN	Capsules, 10,000 i.u. per capsule	Lilly
AVOLEUM	Liquid, 30,000 i.u. per gm. Capsules, 4,500 i.u. per capsule	B.D.H.
β-CAROTENE	Crystals, 1,600,000 i.u. per gm.	Napp
CAROTENE OIL	(1) 0·785 mgm. α- and 1·54 mgm. β-carotene representing 3195 i.u. A per gm. (2) 0·1 mgm. α- and 0·068 mgm. β-carotene representing 1210 i.u. A per gm.	Napp
CAROTENE "TABLOID"	2 mgm. per "tabloid"	B.W.
DAVITAMON A	6,000 i.u. and 60,000 i.u. per mil. Ampoules, 60,000 i.u. in 1 mil oil solution	Organon
ESSOGEN	Capsules, 2,000 i.u. per capsule	Lever
FISH LIVER OIL	Liquid, 200,000 i.u. per gm.	Napp
PREPALIN	Liquid, 72,000 i.u. per mil. Capsules, 24,000 i.u. per capsule. Ampoules, 100,000 i.u. in 1 mil	Glaxo
VITAMIN A	Capsules, 33,000 i.u. per capsule. Ampoules, 100,000 i.u. in 1 mil	Crookes
VITAPEX "PABYRN"	Capsules, 4,500 i.u. per capsule. Ampoules, 75,000 i.u. in 1 mil	Paines & Byrne

Name of Preparation	Description	Makers
	VITAMIN B_1 (ANEURINE)	
BEFORTISS	Ampoules, 5 mgm., 10 mgm. and 25 mgm. ..	Vitamins, Ltd.
BENERVA	Tablets, 1 mgm. and 3 mgm. per tablet. Ampoules 5 mgm. per ampoule. Ampoules Forte, 25 mgm. per ampoule.	Roche Products
BERIN	Ampoules, 5 mgm. and 25 mgm. per ampoule. Tablets, 1 mgm. and 3 mgm. per tablet	Glaxo
BETEBION	Tablets, 1 mgm. per tablet. Ampoules, 2 mgm. in 1 mil. Ampoules "Strong," 10 mgm. in 1 mil.	Merck
BETALIN 1	Capsules, 125 i.u. per capsule	Lilly
BETALIN S	Ampoules, 1 mgm., 6 mgm., 10 mgm. and 30 mgm. per mil. Tablets 0·1, 3 and 6 mgm.	Lilly
BETAXAN	Ampoules, 5 mgm. and 25 mgm. in 1 mil. Tablets, 1 mgm. and 3 mgm. per tablet. Solution, 250 mgm. in 10 mils. Elixir, 0·675 mgm. per drachm	Bayer
CRYSTO-VIBEX	Ampoules, 5 mgm. and 25 mgm. in 1 mil. Tablets, 1 mgm. and 3 mgm. per tablet. Solution, 50 mgm. per mil in 5 mil phials	P. D. & Co.
DAVITAMON B_1	Tablets, 1 mgm. per tablet. Ampoules, 5 mgm. in 1 mil aqueous solution. Davitamon B_1 Forte, Tablets, 3 mgm. per tablet. Ampoules, 25 mgm. per mil aqueous solution	Organon
PULVIS VITAMIN B_1 ..	(1) B.P. standard. (2) Double B.P. standard	Napp
RYZAMIN-B	80 i.u. per gm.	B. W.
THIAMINE CHLORIDE..	Tablets, 1 mgm. and 3 mgm. per tablet. Elixir, 1800 i.u. per fl. oz.	Abbott
VITAMIN B_1 HYDROCHLORIDE	"Hypoloid," 5 mgm. and 25 mgm. in 1 mil. "Tabloid," 3 mgm. and 5 mgm.	B. W.
VITAMIN B_1 "PABYRN"	Ampoules, 5 mgm. and 25 mgm. per ampoule. Tablets, 1 mgm. and 3 mgm. per tablet	Paines & Byrne
VITAMIN B_1	Ampoules, 5 mgm. and 25 mgm. per mil. Tablets, 1 mgm. and 3 mgm. per tablet	B. D. H.
VITAMIN B_1	Ampoules, 5 mgm. and 25 mgm. per ampoule. Capsules, 1 mgm. per capsule. Tablets, 1 mgm. and 3 mgm. per tablet	Crookes Labs.
VITAMIN B_1	Ampoules, 1·5 mgm. and 3 mgm. per ampoule. Tablets, 1·5 mgm. and 3 mgm. per tablet. Injection, 1·5 mgm. and 3 mgm.	A. & H.
	VITAMIN B_2 (RIBOFLAVINE)	
LACTOFLAVINE	Ampoules, 1 mgm. and 5 mgm. per ampoule. Tablets, 1 mgm. and 3 mgm. per tablet	Roche
RIBOFLAVINE	Ampoules, 1 mgm. in 2 mils. Tablets, 1 mgm.	B. D. H.
RIBOFLAVINE	"Tabloid," 1 mgm. and 5 mgm. per "tabloid." "Hypoloid" ampoules, 1 mgm. in 2 mils	B. W.
RIBOFLAVINE	Tablets, 1 mgm. per tablet. Ampoules, 1 mgm.	Crookes Labs.
RIBOFLAVINE	Tablets, 400 Sherman units (G) per tablet ..	Lilly
	VITAMINS B_1 AND B_2 (ANEURINE AND RIBOFLAVINE)	
BENERVA COMPOUND .	Tablets, each containing 1 mgm. B_1, 1 mgm. B_2, and 15 mgm. nicotinamide	Roche
BETALIN COMPOUND ..	Capsules, 333 i.u. B_1 and 40 Sherman units B_2 complex per capsule	Lilly
B & G CAPSULES ..	67 i.u. B_1 and 0·04 mgm. B_2 per capsule	Squibb
B & G SYRUP	50 i.u. B_1 and 0·01 mgm. B_2 per mil..	Squibb
MARMITE	(Unstandardised) B , 8–10 i.u. per gm. (approx.), B_2, 0·033 mgm. per gm. (approx.), Nicotinic acid 0·64 mgm. per gm. (approx.)	Marmite Food Co.
VITAMIN B CAPSULES	150 i.u. B_1, 40 Sherman units B_2	Abbott
VITAMIN B COMPLEX	(1) 100 i.u. B_1 and 0·1 mgm. B_2 per gm.; (2) 200 i.u. B_1 and 0·2 mgm. B_2 per gm.	Napp
YEAST (BREWER'S) ..	Tablets, 15 i.u. B_1, 20 Sherman units B_2	Abbott

Name of Preparation	Description	Makers
	NICOTINIC ACID	
DAVITAMON PP	Tablets, 50 mgm. nicotinic acid in each tablet	Organon
NICOTINIC ACID	Tablets, 50 mgm. per tablet	A. & H.
NICOTINIC ACID	Tablets, 50 mgm. per tablet	Bayer
NICOTINIC ACID ..	"Tabloid" 50 mgm. per "tabloid." "Hypoloid," ampoules, 50 mgm. in 1 mil	B. W.
NICOTINIC ACID ..	Tablets, 50 mgm. and 100 mgm. per tablet..	B. D. H.
NICOTINIC ACID ..	Tablets, 20 mgm., 50 mgm. and 100 mgm.	Lilly
NICOTINIC ACID ..	Tablets, 50 mgm. per tablet. Ampoules, 50 mgm. in 2 mils	Crookes Labs.
NICOTINIC ACID ..	Tablets, 50 mgm. per tablet	P. D. & Co.
NICOTINIC ACID ..	Tablets, 50 mgm. per tablet	Roche
NICOTINIC ACID ..	Tablets, 25 mgm. per tablet	Squibb
NICOTINAMIDE	Ampoules, 50 mgm. per ampoule. Tablets, 50 mgm. per tablet	B. D. H.
NICOTINAMIDE	Tablets, 50 mgm. per tablet. Ampoules, 50 mgm. per ampoule	Roche
PELONIN	Ampoules, 50 mgm. per 2 mils. Tablets, 50 mgm. per tablet	Glaxo
	VITAMIN B_6 (PYRIDOXIN)	
PYRIDOXIN	Ampoules, 50 mgm. per ampoule. Tablets, 10 mgm. per tablet	B. D. H.
PYRIDOXIN	Ampoules, 50 mgm. per ampoule. Tablets, 10 mgm. per tablet	Vitamins, Ltd.
VITAMIN B_6	Ampoules, 50 mgm. in 1 mil. Tablets, 10 mgm. per tablet	Crookes Labs.
	VITAMIN C (ASCORBIC ACID)	
ASCORBIC ACID ..	"Tabloid," 5 mgm., 25 mgm. and 50 mgm. per "tabloid"	B. W.
ASCORBIC ACID ..	Tablets, 0·005 gm., 0·025 gm. and 0·05 gm. per tablet. Injection, 100 mgm. in 2 mils; 500 mgm. in 5 mils	A. & H.
ASCORBIC ACID ..	Tablets, 0·025 gm. and 0·05 gm. per tablet .. Ampoules, 0·1 gm. and 0·5 gm. per ampoule.	B. D. H.
ASCORBIC ACID FOR INFANTS	Tablets, 5 mgm. per tablet	B. D. H.
ASCORBIC ACID ..	Tablets, 50 mgm. per tablet	Vitamins, Ltd.
ASCORBIC ACID	Tablets, 0·05 gm. per tablet	Abbott
CANTAN	Tablets, 5 mgm., 25 mgm. and 50 mgm. per tablet. Ampoules, 0·1 gm. in 2 mils, 0·5 gm. in 5 mils	Bayer
CELIN	Ampoules, 0·1 gm. in 1 mil. Tablets, 0·005 mgm., 0·05 gm. per tablet	Glaxo
CEVALIN	Tablets, 5 mgm. and 25 mgm. per tablet ..	Lilly
DAVITAMON C	Tablets, 5 mgm. and 25 mgm. per tablet. Ampoules, 50 mgm. per mil in aqueous solution, 500 mgm. in 5 mils in aqueous solution	Organon
PLANAVIT C	Tablets, 0·05 gm. and 0·005 gm. per tablet..	May and Baker
REDOXON	Tablets, 25 mgm. and 50 mgm. per tablet. Ampoules, 0·1 gm. per ampoule. Ampoules Forte, 0·5 gm. per ampoule	Roche
REDOXON, "BABIES"	Tablets, 5 mgm. per tablet	Roche
VITAMIN C	Tablets, 5 mgm. and 50 mgm. per tablet. Ampoules, 100 mgm. in 1 mil	Crookes Labs.
VITAMIN C	Tablets, 0·025 gm. and 0·05 gm. per tablet. Ampoules, 0·5 gm. in 5 mils	P. D. & Co.
VITAMIN C CONCENTRATE	0·043 gm. per gm.	Napp
VITAMIN C "PABYRN"	Tablets, 5 mgm., 25 mgm. and 50 mgm. per tablet. Ampoules, 100 mgm. in 2 mils, 500 mgm. in 5 mils	Paines & Byrne

Name of Preparation	Description	Makers
	VITAMIN D	
CALCIFEROL	"Tabloid," 0·1 mgm. and 0·25 mgm. per "tabloid." "Wellcome" solution, 3,000 i.u. per gm.	B. W.
CALCIUM WITH VITAMIN D	Capsules, 250 i.u. per capsule. Liquid, 250 i.u. per fl. drm. Injection, 5,000 i.u. in 1 mil	Crookes Labs.
CALCYDIC	1,500 i.u. per drm. Tablets, 500 i.u. per tablet with dicalcium phosphate	A. & H.
CALFO-RAYOL	Tablets, 660 i.u. with dicalcium phosphate and calcium gluconate	Squibb
CALSOLACT D	Tablets, 1,000 i.u. per tablet	A. & H.
COLLOIDAL CALCIUM WITH OSTELIN	Injection, 5,000 i.u. per mil	Glaxo
DAVITAMON D	5,000 i.u. per mil in oil solution	Organon
DAVITAMON D FORTE	12,500 i.u. per mil in oil solution. Ampoules, 12,500 i.u. per mil	Organon
DAVITAMON D SUPERFORTE	300,000 i.u. per mil. Ampoules, 300,000 i.u. per mil	Organon
DECUFER	Tablets, 500 i.u. with iron, copper and manganese	Organon
OSTELIN	Liquid, 5,000 i.u. per mil. Tablets, 500 i.u. per tablet. Tablets, high potency, 50,000 i.u. per tablet. Emulsion, 100 i.u. per mil	Glaxo
OSTOCALCIUM	Tablets, 500 i.u. per tablet	Glaxo
RADIOSTOL	Solution, 3,000, 100,000 and 200,000 i.u. per gm. Pellets, 3,000 i.u. per pellet	B. D. H.
VIOSTEROL	Liquid, 15,000 i.u. per gm.	A. & H.
VITAMIN D "PABYRN"	Tablets, 2,000 i.u. per tablet. Ampoules, 15,000 i.u. in 1 mil	Paines & Byrne
	VITAMINS A AND D	
ADEXOLIN	Liquid, 12,000 i.u. A, 2,000 i.u. D per mil. Capsules, 4,500 i.u. A, 900 i.u. D per capsule. Emulsion, 600 i.u. A, 100 i.u. D per mil	Glaxo
ADVITA	2,000 i.u. A, 200 i.u. D per capsule	Lever
BYNOL	Liquid, 300 i.u. A, 40 i.u. D per gm.	A. & H.
COD LIVER OIL PERFECTED	Not less than 1,200 i.u. A, 150 to 200 D per gm.	A. & H.
COD LIVER OIL REINFORCED	2,000 i.u. A, 500 i.u. D per mil	May & Baker
COD LIVER OIL "SEVEN SEAS" HIGH POTENCY	2,400 i.u. A, 340 i.u. D per gm.	British C.L.O. Producers
CROOKES EMULSION	2,000 i.u. A, 200 i.u. D per fl. drm.	Crookes Labs.
DAVITAMON A–D	Liquid, 6,000 i.u. A, 5,000 i.u. D per mil. Capsules, 3,000 i.u. A, 2,000 i.u. D per capsule	Organon
DAVITAMON COMFITS	1,500 i.u. A, 1,000 i.u. D per comfit	Organon
DEKADEXOLIN	Ampoules, 60,000 i.u. A, 10,000 i.u. D per mil	Glaxo
HALIBOL	Liquid, 40,000 i.u. A, 6,500 i.u. D per gm. Capsules, 4,500 i.u. A, 900 i.u. D per capsule	A. & H.
HALIBOL CALCIUM	Capsules, 4,500 i.u. A, 900 i.u. D, 5 grs. calcium sodium lactate per capsule	A. & H.
HALIBUT LIVER OIL NATURAL	Liquid, 40,000 i.u. A, 3,000 i.u. D per gm. Capsules, 4,500 i.u. A, 450 i.u. D per capsule	A. & H.
HALIBUT LIVER OIL	(1) Liquid, 30,000 i.u. A, 2,000 i.u. D per gm. (2) From 20,000 to 100,000 i.u. A, from 2,000 to 3,000 i.u. D per gm.	Napp
HALIBUT LIVER OIL	Liquid, 52,000 i.u. A, 2,500 i.u. D per gm. Capsules, 8,800 i.u. A, 425 i.u. D per capsule	Crookes Labs.
HALICALCYNE	Capsules, 5,330 i.u. A, 1,063 i.u. D per capsule, with calcium phosphate	Crookes Labs.
HALIDEXOL	Liquid, 5,740 i.u. A, 382 i.u. D per fl. drm.	Crookes Labs.
HALIVER OIL	Liquid, 50,000 i.u. A, 850 i.u. D per gm. Capsules, 4,500 i.u. A, 450 i.u. D per capsule	Abbott

Name of Preparation	Description	Makers
	Vitamins A and D—*contd.*	
HALIVEROL	Liquid, 27,000 i.u. A, 5,400 i.u. D per gm. Capsules, 4,500 i.u. A, 900 i.u. D per capsule	P. D. & Co.
HEPICOLEUM	Capsules, 4,500 i.u. A, 1,000 i.u. D per capsule	Lilly
NADOLA	Liquid, 27,000 i.u. A, 2,700 i.u. D per gm. Capsules, 4,500 i.u. A, 450 i.u. D	P. D. & Co.
NAVITOL	Liquid, 55,000 i.u. A, 10,000 i.u. D per gm. Capsules, 9,400 i.u. A, 1,700 i.u. D per capsule	Squibb
OLADOL	Liquid, 55,000 i.u. A, 5,500 i.u. D per gm. Capsules, 6,000 i.u. A, 600 i.u. D per capsule	Abbott
RADIOSTOLEUM	Liquid, 15,000 i.u. A, 3,000 i.u. D per gm. Capsules, 4,500 i.u. A, 900 i.u. D per capsule. Injection, ampoules, 75,000 i.u. A, 15,000 i.u. D per gm. in 1 mil ampoules	B. D. H.
RAYOLEX	Tablets, 3,300 i.u. A, 660 i.u. D per tablet	Squibb
SUPER D OIL	65,700 i.u. A, 52,000 i.u. D_3 per gm. Capsules, 11,000 i.u. A, 9,000 i.u. D per capsule	Crookes Labs.
VITAMIN A & D	Capsules, 4,500 i.u. A, 1,000 i.u. D per capsule	Vitamins, Ltd.
VITAPAN	Capsules, 4,500 i.u. A, 1,000 i.u. D per capsule. Compound tablets, 1,500 i.u. A, and 300 i.u. D, with 1/40 grain parathyroid and calcium glycerophosphate	Paines & Byrne
	VITAMIN E	
DAVITAMON E	Capsules, 0·5 mil wheat germ oil per capsule	Organon
EPHYNAL	Tablets, 3 mgm. racemic tocopheryl acetate per tablet. Forte tablets, 20 mgm.	Roche
FERTILOL	Capsules, 5 minims wheat germ oil per capsule	Vitamins, Ltd.
GERMINOL	Capsules, 5 gm. wheat germ oil per capsule	Paines & Byrne
PHYTOFEROL	Capsules, equivalent of 3 mgm. of *dl*-α-tocopherol per capsule	B. D. H.
TRIGOL	Capsules, 5 minims of wheat germ oil	Abbott
VITAMIN E	Capsules, equivalent to 3 mgm. α-tocopherol per capsule	A. & H.
VITAMIN E	"Tabloid," 3 mgm. *dl*-α-tocopherol	B. W.
VITEOLIN	Capsules, 6 mgm. α-tocopherol per 3 minim capsule	Glaxo
WHEAT GERM OIL	Capsules, 1/3 mgm. α-tocopherol per 3 minim per capsule	Crookes Labs.
WHEAT GERM OIL	2 Evans-Burr units per gm.	Lilly
	VITAMIN K	
DAVITAMON K	Liquid, 10 mgm. acetomenaphthone per mil oil solution. Tablets, 10 mgm. per tablet. Ampoules, 10 mgm. menaphthone per mil oil solution	Organon
KAPPAXAN	Tablets, 10 mgm. acetomenaphthone per tablet. Ampoules, 5 mgm. menaphthone	Bayer
KAYVISYN	4-Amino-2-methyl-1-naphthol, 1 mgm. in 1 mil	P. D. & Co.
KLOTOGEN	Liquid, 1,250 units (Almquist method) equivalent to 46,500 Dam units per mil. Capsules, 1,000 units (Almquist method) equivalent to approx. 37,500 Dam units	Abbott
MENAPHTHONE	"Tabloid," 2 mgm. per "tabloid." "Hypoloid" ampoules, 5 mgm. in 1 mil	B. W.
PROKAYVIT	Ampoules, 5 mgm. menaphthone per mil. Tablets 10 mgm. acetomenaphthone per tablet. Solution 10 mgm. capsules in oil solution	B. D. H.
SYNKAVIT	Tablets, 10 mgm. (tetra-sodium salt of 2-methyl-1 : 4-naphthahydroquinone diphosphate), water-soluble vitamin K analogue. Ampoules, 10 mgm.	Roche
VITAMIN K	Capsules, 1/3 mgm. methylnaphthaquinone. Ampoules, 5 mgm. in 1 mil	Crookes Labs.
VITAMIN K "PABYRN"	Ampoules, 10 mgm. menaphthone per mil. Tablets, 10 mgm. acetomenaphthone	Paines & Byrne

Name of Preparation	Description	Makers
	COMBINATIONS	
ABECEDIN	Tablets, 4,500 i.u. A, 50 i.u. B_1, B_2, equal to 2·5 gm. fresh brewer's yeast, 200 i.u. C, 600 i.u. D_3 per tablet. Emulsion, similar constituents per fl. drm., excluding B_2	Napp
ABIDON	Capsules, 4,500 i.u. A, 30 i.u. B_1, 10 Sherman units B_2, 450 i.u. D per capsule	P. D. & Co.
ABIDON WITH VITAMIN C	Capsules, 4,500 i.u. A, 450 i.u. D, 50 i.u. B_1, 20 Sherman units B_2, 200 i.u. C per capsule	P. D. & Co.
A.B.D. CAPSULES ..	5,000 i.u. A, 500 i.u. D, 30 i.u. B_1, 10 Sherman units B_2	Abbott
A.B.D. CAPSULES ..	3,000 i.u. A, 200 i.u. D, 0·3 mgm. B_1 40 Sherman Bourquin units riboflavine per capsule	A. & H.
A.B.D.G. CAPSULES ..	6,600 i.u. A, 1,320 i.u. D, 33 i.u. B_1, 0·02 mgm. B_2 per capsule	Squibb
BEFORTISS	0·3, 1·0, 3 mgm. B_1 with other factors of B complex	Vitamins, Ltd.
BETA-CEVALIN	Capsules, 167 units B_1, 250 units C per capsule	Lilly
COCO-VITAMIN COMPOUND	5,500 i.u. A, 1,300 i.u. D, 16 i.u. D per fl. oz. ..	Lilly
CRYSTO-VIBEX WITH VITAMIN C	Tablets, 0·5 mgm. B_1, 12·5 mgm. C per tablet	P. D. & Co.
DAVITAMON-FIVE ..	Tablets, 1,000 i.u. A, 50 i.u. B_1, 200 i.u. C, 200 i.u. D, 0·5 mgm. nicotinic acid per tablet	Organon
HALIBOL B	Capsules, 4,500 i.u. A, 900 i.u. D, B_1 and B_2 equal to 5 grains dried yeast per capsule	A. & H.
HALIBOL MALT	300 i.u. A, 40 i.u. D per gm.	A. & H.
HALIBORANGE	600 i.u. A, 150 i.u. D, 1 mgm. C per gm. ..	A. & H.
HALIVER MALT WITH VIOSTEROL	28,000 i.u. A, 50 i.u. B_1, 8,000 i.u. D, 50 Sherman units G (B_2) per fl. oz.	Abbott
HEPICOLEUM	Capsules, 4,500 i.u. A, 1,000 i.u. D, per capsule	Lilly
MEDICAPS	Capsules, 4,500 i.u. A, 33 i.u. B_1, 500 i.u. C, 1,320 i.u. D, 22 micro-gm. B_2, vitamin G, the whole of the B_2 complex	Savory & Moore
MULTIVITE	Pellets, 2,500 i.u. A, 160 i.u. B_1, 250 i.u. C, 250 i.u. D_3	B. D. H.
NESTROVITE	Tablets, 2,500 i.u. A, 160 i.u. B_1, 400 gm. C, 500 i.u. D, per tablet. Emulsion, 2,500 i.u. A, 80 i.u. B_1, 300 i.u. C, 500 i.u. D per 5 mils	Roche
OSTOMALT	220 i.u. A, 50 i.u. D per gm. with concentrated orange juice	Glaxo
PENTA-KAPS	4,500 i.u. A, 75 i.u. B_1, 0·01 gm. C, 600 i.u. D, approx. 20 Sherman units G (B_2) per capsule	Abbott
PRIOVIT	1 mgm. B_1, 25 mgm. C, 15 mgm. nicotinamide	Bayer
RADIOSTOLEUM EMULSION WITH VITAMIN C	1,500 i.u. A, 300 i.u. D, 50 i.u. C per gm. ..	B. D. H.
VIMALTOL	46 i.u. A, 2·7–2·9 i.u. B_1, 35 i.u. D per gm. ..	Wander
VITAMIN QUOTA ..	Capsules, 4,500 i.u. A, 450 i.u. D, 100 i.u. B_1, 100γ B_2 per capsule	Crookes Labs.
VITAMIN TONIC "GLANULES"	6,200 i.u. A, 100 Sherman Chase units B_1, 200 i.u. C, 945 i.u. D, B_2 as liver concentrate (1 : 125) 0·060 gm. per "glanule"	Armour

Name of Preparation	Description	Makers
	MISCELLANEOUS PREPARATIONS	
BEMAX	280 i.u. A, 320–420 i.u. B_1, 0·9 mgm. B_2, P.P. factor, 1·1 mgm., 0·45 mgm. B_6, 8 mgm. E, with magnesium, phosphorus, iron and copper	Vitamins, Ltd.
CALSIMIL	Tablets, 500 i.u. D_3 with 5 grains calcium sodium lactate per tablet	B. D. H.
COD LIVER OIL OINTMENT	Fortified with 2,500 i.u. A, 250 i.u. D per gm.	A. & H.
COFRON	Approx. 40 Sherman units G (B_2), approx. 5 i.u. B_1 from liver per capsule, with iron and copper	Abbott
COFRON ELIXIR	Approx. 35 i.u. B_1, approx. 180 Sherman units G (B_2) from liver, per 3 tablespoonsful, with iron and copper	Abbott
COLACT	350 i.u. A, 65 i.u. D per oz.	Glaxo
COMPLEVITE	Tablets, 1,350 i.u. A, 100 i.u. D, with calcium and phosphorus; 67 i.u. B_1 133 i.u. C, with calcium, phosphorus and iron	Vitamins, Ltd.
DEXTRIN MALTOSE No. 4	150 i.u. D per oz.	A. & H.
DEXTRIN MALTOSE No. 6	5 mgm. C per oz.	A. & H.
FAREX	625 i.u. D, 20 i.u. B_1 per oz.	Glaxo
FERROLAC (Full Cream)	165 i.u. D per pint reconstituted	Glaxo
FERROLAC (Fat Modified)	200 i.u. D per pint reconstituted	Glaxo
FERROFAX	28 i.u. B_1 per gm.	Crookes Labs.
F.C.V.D.	62 i.u. D_3 per gm.	Crookes Labs.
GLUCODIN	9 i.u. D per gm.	Glaxo
GLUCOSE B.D.	Powder, 75 i.u. D, 75 i.u. B_1 per fl. drm.	Crookes Labs.
GLUCOSE D TORCH BRAND	250 i.u. D per oz.	A. & H.
HALIMALT	Syrup, 4,300 i.u. A, 420 i.u. D, 44 i.u. B_1 per fl. drm.	Crookes Labs.
HALICITROL	Syrup, 2,600 i.u. A, 315 i.u. D_3, 40 i.u. C per fl. drm.	Crookes Labs.
HEBULON	Capsules, 25 i.u. B_1, B complex, liver extract and ferrous sulphate	Squibb
IBERIN	22 i.u. B_1, 20 Sherman units B (B_2) with iron ammonium citrate and liver concentrate per capsule	Abbott
IRRADEX	6,600 i.u. A, 2,200 i.u. D, 75 i.u. B_1 (with iron and ammonium citrate, manganese citrate and malt extract) per fl. oz.	P. D. & Co.
LACTO-KAOLIN B ..	Kaolin, with 33⅓% lactose, 23 i.u. B_1 per fl. oz.	Crookes Labs.
MINADEX	Syrup, 600 i.u. A, 100 i.u. D per mil	Glaxo
OSTERMILK No. 1 ..	200 i.u. D per pint reconstituted	Glaxo
OSTERMILK No. 2 ..	165 i.u. D per pint reconstituted	Glaxo
PREGNAVITE	Tablets, same constituents as Complevite ..	Vitamins, Ltd.
RADIOMALT	A, B_1, B_2 and D	B. D. H.
VALOGEN	Extract of yeast with added B_1, and nicotinamide with salts of iron, copper, cobalt and manganese	B. D. H.
VENTRON	22 i.u. B_1, 5 Sherman units B_2 per capsule, with Ventriculin and Naferon (iron and sodium citrate)	P. D. & Co.
VIOZIN OINTMENT ..	500 i.u. D per gm.	Glaxo
	VITAMIN P	
PERMIDIN	0·15 gm. per tablet	Glaxo
VITAMIN P	Ampoules, 10 mgm. hesperidin in 1 mil	Crookes Labs.

Makers and Suppliers

The following is a list of the names of makers, with their addresses, of the products mentioned in the table:

ABBOTT—Abbott Laboratories (England), Ltd., Wadsworth Road, Perivale, Middlesex

A. & H.—Allen & Hanburys, Ltd., Bethnal Green, London, E.2

ARMOUR—The Armour Laboratories (Armour & Co., Ltd.), Thornton House, Finsbury Square, London, E.C.2

BAYER—Bayer Products, Ltd., Africa House, Kingsway, London, W.C.2

BRITISH C.L.O. PRODUCERS—British Cod Liver Oil Producers (Hull), Ltd., St. Andrew's Dock, Hull

B.D.H.—The British Drug Houses, Ltd., Graham Street, City Road, London, N.1

B.W.—Burroughs Wellcome & Co., 183/193, Euston Road, London, N.W.1

CROOKES LABS.—The Crookes Laboratories (British Colloids, Ltd.), Gorst Road, Park Royal, London, N.W.10

LILLY—Eli Lilly & Co., Ltd., Basingstoke, Hants.

GLAXO—Glaxo Laboratories, Ltd., Greenford, Middlesex

LEVER—Lever Brothers & Unilever, Ltd., Unilever House, Blackfriars, E.C.4

MARMITE FOOD EXTRACT CO.—The Marmite Food Extract Co., Ltd., Twenty Steps, Beare Green, Dorking, Surrey

MAY & BAKER—Pharmaceutical Specialities (May & Baker), Ltd., Dagenham, Essex

MERCK—Savory & Moore, Ltd., Standard Works, Lawrence Road, Tottenham, N.15

NAPP—H. R. Napp, Ltd., 3 & 4, Clements Inn, London, W.C.2

ORGANON—Organon Laboratories, Ltd., Brettenham House, Lancaster Place, W.C.2

PAINES & BYRNE—Paines & Byrne, Ltd., Pabryn Laboratories, Bilton Road, Greenford, Middlesex

P. D. & CO.—Parke, Davis & Co., Beak Street, Regent Street, London, W.1

ROCHE—Roche Products, Ltd., Broadwater Road, Welwyn Garden City, Herts.

SQUIBB—Savory & Moore, Ltd., Standard Works, Lawrence Road, Tottenham, N.15

VITAMINS, LTD.—Vitamins, Ltd., 23, Upper Mall, Hammersmith, London, W.6

WANDER—A. Wander, Ltd., 184, Queen's Gate, S.W.7

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